§ 1010.5 Exemptions for products intended for United States Government use.

* * * * *

(c) * * *

(12) Such other information required by regulation or by the Director, Bureau of Radiological Health, to evaluate and act on the application. Where such information includes nonclinical laboratory studies, the information shall include, with respect to each nonclinical study, either a statement that each study was conducted in compliance with the requirements set forth in Part 58 of this chapter, or, if the study was not conducted in compliance with such regulations, a statement that describes in detail all differences between the practices used in the study and those required in the regulations. When such information includes clinical investigations involving human subjects, the information shall include, with respect to each clinical investigation, either a statement that each investigation was conducted in compliance with the requirements set forth in Part 56 of this chapter, or a statement that the investigation is not subject to such requirements in accordance with §§ 56.104 or 56.105 and a statement that each investigation was conducted in compliance with the requirements set forth in Part 50 of this chapter.

* * * * *

Effective date. This regulation shall become effective July 27, 1981.

(Secs. 406, 408, 409, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701(a), 706, and 801, 52 Stat. 1049–1053 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–560, 562–574 (21 U.S.C. 346, 346a, 348, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371(a), 376, and 381); secs. 215, 301, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n))

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 81-2587 Filed 1-21-81; 8:45 am]

BILLING CODE 4110-03-M

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21 CFR Parts 16 and 56

[Docket No. 77N-0350]

Protection of Human Subjects; Standards for Institutional Review Boards for Clinical Investigations

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA or agency) is establishing standards governing the composition, operation, and responsibility of institutional review boards (IRBs) that review clinical investigations, involving human subjects, conducted pursuant to requirements for prior submission to FDA or conducted in support of applications for permission to conduct further research or to market regulated products. These regulations and the protection of human research subjects regulations adopted by the Department of Health and Human Services (HHS or Department) published in the January 26, 1981 issue of the **Federal Register**, establish a common framework for the operation of IRBs that review research funded by HHS and research conducted under FDA regulatory requirements. Compliance with these regulations is intended to provide protection of the rights and welfare of human subjects involved in clinical investigations.

EFFECTIVE DATE: July 27, 1981.

FOR FURTHER INFORMATION CONTACT: John C. Petricciani, Office of the Commissioner (HFB–4), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301–496–9320.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of August 8, 1978 (43 FR 35186), FDA published proposed standards for IRBs for clinical investigations. Interested persons were given until December 6, 1978 to submit written comments on the proposal. By notice in the **Federal Register** of December 15, 1978 (43 FR 58574), FDA extended the comment period to June 6, 1979. During the comment period, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) submitted its report and recommendations on IRBs and informed consent, and that document was published in the **Federal Register** of November 30, 1978 (43 FR 56174). In its report, the National Commission recommended revision of the current HHS IRB regulations (45 CFR Part 46). On August 14, 1979 (44 FR 46799), FDA withdrew the August 8, 1978 proposal and published a revised proposal that it had developed in conjunction with HHS in response to the recommendations made by the National Commission.

In addition, the agency held three hearings under § 15.1(a) (21 CFR 15.1(a)) of the administrative practices and procedures regulations in: (1) Bethesda, Maryland, on September 18, 1979; (2) San Francisco, California, on October 2, 1979; and (3) Houston, Texas, on October 16, 1979. These hearings were intended to provide an open forum to present views on the regulations and to foster greater consideration of the proposal among the scientific community, regulated industry, and the public. (Transcripts of these hearings are on file with the Dockets Management Branch (formerly the Hearing Clerk's office) (HFA–305), FDA.)

For the reasons set forth in paragraph 1, the sections of the regulation have been reorganized and renumbered to be parallel with the Department's regulations. The following table correlates the new sections with those proposed.

New section	Old section
56.101	56.1.
56.102	56.3.
56.103	56.5.
56.104	No corresponding section.
56.105	56.6.
56.107	56.21, 56.25, 56.26, and 56.34.
56.108	56.80, 56.81, and 56.87.
56.109	56.82 and 56.87.
56.110	56.83.
56.111	56.86.
56.112	56.8, 56.9, 56.87, and 56.90.
56.113	56.90.
56.114	56.9.
56.115	56.15, 56.21, 56.25, 56.185, and 56.195.
56.120	No corresponding section.
56.121	56.202, 56.206, and 56.210.
56.122	56.213.
56.123	56.219.
56.124	56.215.

FDA will seek Office of Management and Budget (OMB) clearance of the reporting and recordkeeping requirements contained in these regulations prior to the effective date. If OMB does not approve the reporting and recordkeeping requirements without change, the agency will revise the regulations to comply with OMB's recommendations.

The agency received 145 comments on the original proposal and 179 comments on the reproposal. In addition, approximately 100 people appeared at the three public hearings. Following is a summary of the significant comments received and FDA's response to them:

General Comments

1. One of the overriding themes in the comments was that the agency should adopt the same final regulations as the Department.

FDA agrees that the Department's and the agency's regulations should be as consistent as possible, and it recognizes that if such consistency is achieved, IRBs that deal with both FDA and other HHS components will be able to follow a uniform standard. Therefore, FDA participated with other components of the Public Health Service in an intra-departmental task force whose goal was to achieve the maximum degree of

consistency possible in the Department's and the agency's IRB and informed consent regulations. Drawing heavily on the comments received by both HHS and FDA, the task force made substantial progress toward achieving its goal.

As a result, the structrual and functional requirements for IRBs in FDA's regulations are identical to those in the Department's regulation. FDA and HHS have adopted the same definitions for "institution" (§ 56.102(d)) and "minimal risk" (§ 56.102(h)), and identical provisions relating to IRB membership (§ 56.107), IRB functions and operations (§ 56.108), IRB review of research (§ 56.109), expedited review (§ 56.110), criteria for IRB approval of research (§ 56.111), review by an institution (§ 56.112), suspension or termination of IRB approval of research (§ 56.113), cooperative research (§ 56.114), and records (§ 56.115). In addition, the organization of the two sets of IRB regulations is now consistent.

While exact congruity between the Department's and the agency's regulations is not possible because of differences in statutory authority and scope of activity, FDA believes that these regulations are as identical as possible with the regulations that are being adopted by HHS for the protection of human subjects who participate in research funded by the Department.

2. Several comments suggested that FDA adopt the assurance mechanism that is contained in the Department's regulations.

FDA has decided not to adopt this mechanism. Although consistency with the Department's regulations is important, the agency finds that other factors make adoption of the assurance mechanism inappropriate. FDA has determined that the benefits of the entrance into the assurance process of the IRBs that are subject to FDA jurisdiction, but not otherwise to HHS jurisdiction, do not justify the increased administrative burdens that would be placed on institution by requiring them to submit assurance materials to the Department's Office of Protection from Research Risks (OPRR), or the increased burden on the Government of processing those assurance submissions. FDA will rely instead on the dissemination of these regulations and on appropriate educational efforts, together with inspections of IRBs, to assure compliance by IRBs with these regulations.

3. One comment stated that while there should be an organized group to establish guidelines, standards, procedures, and educational activities that assure the high quality and performance of IRBs, that group should not come from within the Government. The comment stated that institutions themselves, or other interested parties independent of the Federal Government, would organize for these purposes.

While FDA would welcome such an organization, the agency points out that none presently exists. As discussed in paragraph 8 of this preamble, FDA has been charged by Congress with the responsibility of protecting the rights and welfare of human subjects who participate in research that comes within the agency's jurisdiction. Therefore, it is necessary for the agency to publish these regulations to fulfill that responsibility.

4. Three comments stated that FDA does not have legal authority to adopt these regulations. Two comments stated that section 701(a) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 371(a)) cannot be used as a grant of authority to regulate any subject the agency selects. The comments argued that the subject matter of regulations must be within the substantive authority of the agency, and that there is no mention anywhere in the act that the agency can require that clinical investigations be reviewed by an IRB. Two comments suggested that the proposed regulations should therefore be republished as guidelines.

FDA rejects these comments. The agency presented a thorough discussion of its authority to require IRB review in the preamble to the August 8, 1978 proposal at 43 FR 35197. As the agency pointed out in that preamble, its authority to adopt these regulations is derived from several sections of the act.

In section 520(g)(3)(A)(i) of the act (21 U.S.C. 360j(g)(3)(A)(i)), congress directed the agency to include in its investigational device exemption (IDE) regulations (21 CFR Part 812) a requirement that an applicant for an IDE submit the plan for research to the local "institutional review committee" that "* * * has been established in accordance with regulations of the [Commissioner] * * *." Under § 56.102(e) of these regulations, "institutional review committee" is synonomous with "institutional review board."

Although there are no corresponding explicit provisions with regard to the other clinical investigations covered by these regulations, the Supreme Court has recognized in *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 653 (1973), that FDA has authority that "is implicit in the regulatory scheme, not spelled out *in haec verba*" in the statute. As stated in *Morrow* v. *Clayton*, 326 F.2d 36, 44 (10th Cir. 1963):

> However, it is a fundamental principle of administrative law that the powers of an administrative agency are not limited to those expressly granted by the statutes, but include, also, all of the powers that may be fairly implied therefrom.

See *Mourning* v. *Family Publications Service, Inc.*, 411 U.S. 356 (1973); see also *National Petroleum Refiners Association* v. *FTC*, 482 F.2d 672 (D.C. Cir. 1973).

Sections 505(i), 507(d), and 520(g) of the act (21 U.S.C. 355(i), 357(d), and 360j(g)) require that the agency issue regulations that establish the conditions under which drugs and devices will be available for investigational use. Those sections of the act direct the agency to issue regulations to protect the public health in those investigations. FDA has determined (43 FR 35197) that a requirement of IRB review of an investigation is essential to safeguard the rights and welfare, and consequently, the health, of the human subjects involved in the study.

In addition, sections 505(j)(1) and 507(e) of the act require that the regulations adopted under sections 505(i) and 507(d) reflect due regard for the ethics of the medical profession and the interests of patients. There is a similar requirement in section 520(g)(1) of the act that the investigations conducted under that section be consistent with ethical standards. Because IRB review is intended to focus on the ethical acceptability of studies and on the protection of human subjects, FDA believes that the requirement of IRB review will ensure that there is due regard for the ethics of the medical profession and for the interests of patients in the investigations covered by these regulations.

Finally, under section 701(a) of the act, the agency is empowered to issue regulations for the efficient enforcement of the act. In assessing the validity of regulations issued under section 701(a), the basic question is whether the statutory scheme as a whole justifies promulation of the regulation. *National Confectioners Association* v. *Califano*, 569 F.2d 690, 693 (D.C. Cir. 1978). As explained in the preamble to the August 8, 1978 proposal, IRB review is very important in helping FDA to assure that the rights and welfare of human subjects are protected in clinical investigations regulated by the agency because IRBs require modifications in or disapproval of those clinical investigations that present unreasonable risk in relation to the benefits and knowledge to be gained. See also 43 FR 35197. Therefore,

the agency has determined that these regulations are essential to enforcement of the agency's responsibilities under sections 406, 409, 501, 502, 505, 506, 507, 510, 513, 514, 515, 516, 518, 519, 520, 706, and 801 of the act, as well as the responsibilities of FDA under sections 301, 351 and 354–360F of the Public Health Service Act.

5. Several comments questioned how the regulations would affect the interaction in clinical investigations of IRBs, sponsors, monitors, and ivestigators. One comment stated that these regulations may make an IRB feel liable for tasks that are the responsibility of a sponsor.

The IRB regulation is one of five regulatory elements in FDA's bioresearch Monitoring Program. That program is designed to assure the quality and integrity of the research that is subject to the agency's jurisdiction. In addition to the two FDA regulations published in this issue, the Bioresearch Monitoring Program includes proposed regulations to establish obligations of clinical investigators (proposed August 8, 1978 (43 FR 35210)), obligations of sponsors and monitors of clinical investigations (proposed September 27, 1977 (42 FR 49612)), and good laboratory practice regulations (21 CFR Part 58).

The agency has attempted to include in each bioresearch monitoring regulation only the specific obligations of the entity that the regulation covers. Although the IRB regulations obviously include matters of interest to both sponsors and clinical investigators, an IRB should have no problem determining the boundaries of its obligations.

The agency recognizes, however, that the bioresearch monitoring entities are intimately related and interdependent, and that there are certain well-established relationships among IRBs, clinical investigators, and sponsors of clinical investigations. Consequently, the agency believes that it should not impose any unnecessary requirements that would disrupt those relationships. For example, because IRBs usually do not have any direct contact with sponsors, FDA has eliminated from these regulations any requirement that an IRB contact a sponsor. The clinical investigator has the responsibility of keeping the sponsor informed of IRB actions.

6. Several comments claimed that the proposed regulations contained unnecessary, irrelevant, and repetitive rules which would serve as a deterrent to research.

These regulations are intended to establish the basic framework for IRBs and their parent institutions. They differ from those proposed in 1978 and 1979 in that FDA has included in the final regulations only the essential organizational and procedural requirements for IRBs and has not specified in detail how those requirements are to be met. Because of the great diversity in institutions, research activities, and organizational structures covered by these regulations, FDA has decided that there must be sufficient flexibility in the regulations to allow IRBs and their parent instituitions to meet these requirements in a manner that best suits their organizational needs. As a result of this approach, FDA has accepted the thrust of the comments and, as detailed in responses to comments regarding specific sections of the proposal, has deleted a number of the proposed provisions from these final regulations.

7. Several comments suggested that the proposed regulations be withdrawn because they offer no real protection to anyone.

FDA rejects this suggestion. These rules provide minimum standards for review of clinical investigations by IRBs to ensure that the rights and welfare of human subjects will be protected in the investigation. Once these regulations are adopted, if institutions select reasonable and appropriate individuals for the IRBs, the IRB review process will provide a significant safeguard for human subjects in research.

8. Other comments suggested that the objectives of these regulations could be achieved through existing common law and State regulations.

FDA disagrees with these comments. Congress has charged the agency with the responsibility of protecting the rights and welfare of human subjects who participate in research that comes within FDA's jurisdiction. Consequently, the agency cannot rely on existing common law or State regulations. The only way the agency can assure that adequate protections exist nationally is by adopting regulations that define what protections are necessary and that require that those protections be extended to all human subjects in research within the agency's jurisdiction. FDA is adopting these regulations because only through properly constituted and well-functioning IRBs can the agency be assured that the rights and welfare of human subjects are being protected before a study starts, and that the study is ethically acceptable.

9. One comment stated that Congressional and FDA investigations have amply demonstrated that some IRBs, if left free from systematic oversight, will not adequately carry out their obligations. Several other comments stated that what is needed is an open and trusting relationship between FDA and IRBs.

FDA believes that these regulations, when coupled with FDA's inspection program, strike the appropriate balance between the conflicting approaches to the regulation of IRBs presented by these contrasting comments. The Federal Government cannot bear alone the burden of protecting the rights and welfare of human subjects. Investigators, institutions, and sponsors must share in this responsibility. If IRBs follow these regulations, they will protect human subjects. However, if the agency finds serious deficiencies in the IRB review process at a particular institution, the agency will take appropriate action, as provided for in these regulations.

10. A few comments raised questions about the costs of IRB review. The comments pointed out that there are administrative costs associated with an IRB, and they raised questions about who would pay those costs. One comment stated that a sponsor should be able to provide compensation to IRBs, provided that it does not participate in the selection of IRB members.

FDA recognizes that there are administrative costs associated with IRB review. Because, under these regulations, there is no single administrative model, for example, a single institution may have multiple IRBs, or a single IRB may review studies for several institutions, FDA believes that it is inappropriate for it to prescribe a method for reimbursement for administrative costs, and that the parties themselves should resolve this matter. FDA's statement in the preamble to the August 8, 1978 proposal regarding proposed § 56.26(a) that IRB members should not be compensated for services did not mean that administrative costs such as consultation fees, travel expenses, typing services, paper and supplies, meeting rooms, etc., could not be paid by the sponsor or institution.

11. One comment suggested that institutional review would significantly increase the costs of clinical investigations.

The agency rejects this comment. FDA estimates the cost of IRB review of a clinical investigation to be approximately $100. Consequently, compared to the total costs of a clinical investigation, the costs of IRB review are insignificant.

12. One comment criticized the absence of data in the Economic Impact Assessment (EIA) of the proposed regulation, but did not dispute the

agency's conclusion that the regulation would not cause a major impact.

The EIA stated that the IRB regulation would "provide for extension of an IRB concept to areas where it has not previously been used" (i.e., to studies involving noninstitutionalized subjects) and increase some of the review group's administrative activities, but that these additional costs would not approach the $100 million cost threshold for a major impact. The data underlying that conclusion follow.

The agency estimates that 2,000 IRBs are reviewing or have reviewed studies submitted for FDA approval. Approximately 500 of these IRBs have submitted a *General Assurance* to HHS that they are in compliance with departmental regulations. An agency study (Office of Planning and Evaluation Study 47, "Results of the Institutional Review Board's Pilot Compliance Program," April 1978) found that these IRBs review an average of 11 studies per month, amounting to a total of 66,000 reviews annually. The study also found that IRBs that had not submitted a *General Assurance* to HHS review an average of five studies per month, amounting to a total of 90,000 reviews annually, and that more than 50 percent of these IRBs were already in compliance with the administrative and procedural requirements.

Institutional Review boards will incur some additional costs, in part for more thorough review and followup of investigations and in part because there will be additional studies subject to IRB review. FDA estimates that the incremental costs will be $7.5 million. This estimate was derived by assuming that the expansion of IRB review to studies using noninstitutionalized subjects will add one-third, or $52,000, more reviews. According to one estimate, a review by an IRB with a *General Assurance* now costs about $100 (William A. Check, "Protecting and Informing Human Research Subjects," *JAMA*, 243 (1980), 1985–1993.) Thus, the costs of the added reviews are $5.2 million. If we further assume that the average IRB without a *General Assurance* now spends $75 per review, the added cost to bring their reviews into compliance with agency regulations is $2.3 million. This $75 average cost derives from the assumption that the IRBs already in compliance (50%) spend $100 per review and the generous assumption that the remaining IRBs (50%) will double their present review costs to come into compliance.

The EIA also attributed potential agency compliance costs to the regulation. However, there will be little, if any, incremental costs to the agency, given present budgetary constraints.

13. One comment requested that these regulations grant IRB members limited liability in the case of malpractice suits.

FDA lacks the authority to grant limited liability to IRB's or their members. That authority resides in Congress and in the State legislatures. Although it is impossible to limit liability or to ensure against law suits, the agency believes that the chances for a successful suit against an IRB or its members are greatly diminished if the IRB has complied with these regulations and any applicable State law in reviewing the proposed research. See, e.g., *Davis* v. *Marathon Oil Co.*, 64 Ill. 2d 380, 356 W.E. 2d 93 (1976).

14. Several comments questioned the applicability of these regulations to studies conducted outside the United States. A few comments stated that standards of protection for human subjects may and do vary from country to country, and that the United States should not impose its standards on other countries when the human subjects come from those foreign countries in which the studies are being conducted.

FDA agrees with the comments and notes that its policy regarding investigational studies involving drugs and biological products is set forth in § 312.20 *Clinical data generated outside the United States and not subject to a "Notice of Claimed Investigational exemption for a New Drug"* (21 CFR 312.20). The policy regarding foreign studies and the background to § 312.20 was set forth in detail in the preambles to the proposed and final regulations. See 38 FR 24220 (September 6, 1973) and 40 FR 16053 (April 9, 1975). The agency's policy regarding studies of investigational devices conducted outside the United States is similar to that for drugs and biological products and is discussed in the preamble to the recent proposal entitled "Proposed Procedures for the Premarket Approval of Medical Devices," published in the **Federal Register** of December 12, 1980 (45 FR 81769). Section 814.15 of that proposal states the agency's policy concerning devices.

The Proposed Regulation

15. Numerous comments objected to the statement in proposed § 56.1 *Scope* (§ 56.101 in the final regulations) that compliance with these regulations would help to assure the quality and integrity of data submitted to FDA. These comments argued that it is neither the responsibility nor within the competence of an IRB to assure the quality and integrity of data. The comments stated that the primary functions of an IRB are to assure the ethical acceptability of a particular study and to assure that human subjects are adequately protected. One comment argued that IRBs would be converted into consultants for sponsors if they were required to review the quality and integrity of data. A number of comments asserted that review of the validity and integrity of data on an ongoing basis would be an undue burden on IRBs. A number of comments objected on similar grounds to including review of research methods among the criteria for approval of a clinical investigation. The comments argued that the IRB should focus on its primary task of risk assessment, and that the scientific evaluation, validation, and justification necessary for a study should be the obligation of the clinical investigator responsible for the study and of the sponsor.

During the process of reviewing the comments and developing IRB regulations with other components of the Department, FDA became convinced that a number of IRB obligations included in the 1978 and 1979 proposals were inconsistent with the generally accepted view of the scope of IRB review. Consequently, the agency decided to reconsider whether to impose those obligations. One of the obligations most difficult to delineate was the extent to which an IRB must consider the scientific aspects of a research proposal. FDA acknowledges that the primary responsibilities of an IRB are to assure that human subjects are adequately protected, are not exposed to unnecessary risks, and are provided with enough information about a study so that they can give effective informed consent. However, the agency believes that is is impossible to divorce completely considerations of science from those of ethical acceptability and of protection of human subjects. Some type of scientific review is necessary to determine whether the risk to which subjects are exposed is reasonable.

Thus, FDA has decided to delete from § 56.101 all references to any responsibility on the part of IRBs to assure the validity and reliability of data, because the agency is concerned that reference to such an obligation could be interpreted as imposing on IRBs the obligation to exercise primary scientific review responsibilities for clinical studies. IRBs have no such obligation. However, FDA believes that the IRB, the institution, and the clinical investigator share an obligation to assure that a review of the scientific merits of a proposal is conducted. FDA believes that an IRB cannot reasonably

review a study or make a valid risk assessment, unless there has been a positive assessment of the scientific merits of the research.

16. Numerous comments objected that proposed § 56.1 did not limit the scope of IRB review of clinical investigations to exclude those that are conducted outside of an institution. These comments suggested that the other elements of FDA's Bioresearch Monitoring Program provide sufficient protection for human subjects who are not institutionalized.

FDA rejects these comments and declines to change § 56.101 in response to them. Human subjects, whether institutionalized or not, are entitled to the protections that these regulations offer. The agency agrees that the other elements of the Bioresearch Monitoring Program provide important protections to human subjects. However, as the agency pointed out in paragraph 5, the elements of that program are closely related and interdependent. IRB review is necessary to ensure that the rights and welfare of human subjects are protected, and that the subjects are adequately informed prior to the start of a study.

17. One comment questioned whether these regulations would require physicians practicing in their offices to obtain IRB review of their proposed clinical investigations. Another comment suggested that physicians practicing in their offices should have a centrally located IRB available for their use.

Physicians who practice in their offices and who wish to conduct clinical investigations for a sponsor or as sponsor-investigators are required to comply with these regulations to obtain a research permit. The agency recognizes, however, that in some instances such physicians (and other health professionals who would otherwise qualify for a research permit) may not be affiliated with an institution or have direct access to an IRB. In those instances, FDA advises that several options are available to the physician. A sponsor-investigator who is unaffiliated with an institution with an IRB can comply with this requirement by obtaining review at an institution whose IRB conforms with these regulations or by submitting the research proposal to an IRB created under the auspices of a local or State government health agency, a community hospital, a private or public medical school, a county or State medical society, the State medical licensing board, an independent nonprofit group such as a foundation or society interested in a particular health concern, e.g., kidney disease or family planning, or an organization involved in intergroup communications, e.g., the American Arbitration Association. A private physician who wants to conduct clinical research for a sponsor, in addition to these options, may use an IRB created by the sponsor.

18. One comment suggested that optometrists in private practice be exempted from the requirements of these regulations.

FDA rejects this suggestion. The agency believes that human subjects involved in any clinical investigation subject to FDA jurisdiction (except for those specifically exempted) need the protections that these regulations afford, regardless of whether the study is being conducted by optometrists, medical doctors, dentists, or other health professionals.

19. Several comments objected to the inclusion of cosmetic studies within the scope of these regulations. These comments pointed out that cosmetic studies are not subject to submission to the agency for premarket approval and therefore should not be subject to a requirement of IRB review.

FDA agrees with the comments and has modified § 56.101 to exclude cosmetic studies from the scope of the IRB regulations.

20. Several comments urged that FDA not include over-the-counter (OTC) drugs in the scope of Part 56.

In the preamble to the 1978 proposal at 43 FR 35189, FDA announced:

> The Commissioner believes the purposes and processes of IRB review are now so widely accepted, and its value so generally recognized, that all clinical investigations should undergo such review unless circumstances clearly make it unnecessary, or infeasible, or contrary to the patient's interest.

Consistent with that determination, FDA has decided to require IRB review of all clinical investigations (except those exempted under § 56.104 or for which a waiver has been obtained under § 56.105) of test articles that are intended to be submitted to the agency in support of an initial or supplemental research or marketing permit. However, because the agency recognizes the lower risk associated with studies of marketed OTC drugs, and because the agency wishes to minimize the administrative burden created by these regulations, FDA has decided to include studies with marketed OTC drugs, and other drug or biologic studies for which an IND is not required (e.g., bioavailability studies with a marketed drug), on the list of procedures that can receive expedited review.

21. One comment argued that FDA has no authority to require IRB review of OTC drugs because OTC drugs are not unapproved new drugs within the meaning of section 505(i) of the act.

That an OTC drug is being reviewed under the procedures established in 21 CFR Part 330 does not mean that the drug is not an unapproved new drug under section 505 of the act. One of the purposes of establishing the OTC review was to make certain scientific and legal determinations with regard to a drug's status under section 505 of the act. In making those determinations, under OTC review procedures, the agency will consider data on a drug ingredient that interested persons may submit. To develop these data, investigators may conduct tests for submission to the agency that may present risks to human subjects. These tests should therefore be subject to review by IRB's. As discussed in paragraph 4 of this preamble, the agency has authority under section 701(a) of the act to promulgate regulations to implement section 505 (as well as other sections of the act) that requires such review of these studies. Therefore, it is within the legal authority of the agency to include investigations of drugs under consideration in the OTC review within these regulations.

22. A few comments objected to the inclusion of low risk or no risk studies within the scope of these regulations. The comments suggested that because risk is so low in these studies, and because FDA has rules governing informed consent, no IRB review is needed. A few comments argued that IRB review would not add any protections for human subjects in low risk studies.

FDA believes IRBs should review studies even when there is minimal risk, to assure that (1) there is, in fact, only minimal risk; (2) adequate information is given to the subject or a legally authorized representative, so that effective informed consent can be given; (3) the study is ethically acceptable; and (4) the study complies with the requirements in these regulations. FDA also points out that it has modified these regulations to provide for expedited review of certain studies involving minimal risk (§ 56.109). A notice listing the eligible categories of studies is published elsewhere in this issue of the **Federal Register.**

23. One comment suggested that use of an investigational drug in an emergency situation should be exempted from IRB review.

The agency recognizes that there is a practical need to provide a mechanism for the emergency use of a test article in a single patient. After examining various options, FDA has elected to exempt the emergency use of test articles from the

IRB review requirement and so provides in new § 56.104(c). The agency advises, however, that it views emergency use of a test article as being an uncommon occurrence, and that it will examine the circumstances of emergency use on a case-by-case basis to assure that emergency procedures are not being used to circumvent IRB review. FDA also points out that it has conditioned this exemption on a report of the emergency use to the IRB within 5 working days of its occurrence. FDA would expect that the IRB that receives the report by a clinical investigator on an emergency use, as required by § 56.104(c) and § 50.23(c), will examine each case to assure itself and the institution that the emergency use of the test article was justified. FDA also advises that while it has exempted emergency use of test articles from the requirement of prospective IRB review, this exemption does not release the clinical investigator from any other obligation imposed by other regulations or by the institution in which the emergency use is undertaken. Finally, the agency advises that a "subsequent use," as referred to in the regulation, would be any use of the test article that occurs more than 5 days after its initial emergency use.

24. On its own initiative, FDA has eliminated proposed § 56.3(f) defining "institutionalized subject" because that term does not appear anywhere in Part 56. FDA has eliminated the definition of "person" in proposed § 56.3(i) because that term is used in these regulations only to denote an individual.

25. Several comments stated that the proposed definition of "clinical investigation" in proposed § 56.3(c) (now § 56.102(c)) is too broad and confusing.

FDA disagrees. The definition was drafted to include all studies within FDA's jurisdiction that are subject to the requirements of prior submission to the agency or that may be submitted to the agency in support of a research or marketing permit. The comments are rejected.

26. One comment stated that proposed § 56.3(c) should clearly state that a clinical investigation is always medical in nature and always involves human subjects.

FDA has attempted, whenever possible, to make the IRB regulations identical with those of the Department. To facilitate this goal, FDA has not defined "clinical investigation" to include only those studies that are medical in nature. As a result, this term is interchangeable with the term "research" as that term is defined by HHS. Because these terms are interchangeable, the same wording can be used in provisions in both FDA's and the Department's regulations. Section 56.102(c) in the final regulations is revised to clarify this fact and to conform with the HHS regulations.

FDA points out that § 56.102(c) already states that human subjects must be involved in a "clinical investigation."

27. Two comments stated that proposed § 56.3(d) defining "institution" was too broad.

As stated in paragraph 1 of this preamble, FDA has revised § 56.102(d) to conform its definition of "institution" with that of the Department. "Institution" is now defined as any public or private entity. Although this definition is perhaps even broader than the proposed definition, the definition itself does not define the scope of those regulations. That scope is clearly set out in § 56.101. IRB review will now be required for all clinical investigations that support applications for research or marketing permits for products regulated by FDA. As noted in the 1978 proposal, it may no longer be strictly appropriate to call the process "institutional review" because the process is no longer tied to "institutions" as they were previously defined (43 FR 35188). Because the concept of institutional review is well understood by the research community, and because no better terminology has been suggested, the terminology has been retained.

28. One comment suggested that contract laboratories should be added to the proposed definition of "institution."

The revised definition of "institution" in § 56.102(d) includes any entity. A contract laboratory clearly would come within the purview of the regulations.

29. Two comments expressed concern about including manufacturers in the definition of "institution." One comment stated that the definition would include manufacturers who use their employees as subjects in the course of routine product testing, even though the manufacturers did not intend to use the data from that testing in support of a research or marketing permit.

The intent of these regulations is to protect human subjects in clinical investigations that are subject to FDA jurisdiction. Therefore, the definition of "institution" must be broad enough to include manufacturers who use employees as test subjects in such research. However, only clinical investigations that are regulated by FDA under sections 505(i), 507(d), and 520(g) of the act or that are intended to support applications for research or marketing permits for products regulated by FDA are within FDA jurisdiction. Therefore, routine product testing, in which the data are not intended to be used in support of a research or marketing permit or to support the safety and effectiveness of a regulated article, would not be subject to these regulations.

30. On its own initiative, FDA has modified the definition of "institutional review board" in proposed § 56.3(e) (now § 56.102(g)) to clarify that the primary purpose of an IRB is to assure the protection of the rights and welfare of human subjects.

31. One comment stated that HHS and FDA should have a common suitable definition of "institutional review board."

FDA points out that HHS has chosen not to include a definition of "institutional review board" in its regulations. FDA believes, however, that the agency's definition is compatible with the traditional use of the term by HHS and the biomedical community. FDA concludes that its definition of "institutional review board" in § 56.102(g) is suitable.

32. One comment suggested that FDA and HHS should collaborate on common terminology and definitions for the terms "subject" and "human subject."

The scope of research supported by the Department includes behavioral research that FDA does not regulate. At the same time, the scope of research regulated by FDA includes veterinary research that HHS, other than FDA, does not regulate and that, for obvious reasons, are not subject to these regulations. Therefore, it is appropriate for FDA to use the term "human subject" to clarify the scope of the regulation, and to define the scope of the term "human subject" as in § 56.102(e) more narrowly than has HHS. Section 56.102(e) has been revised to relate specifically to the types of research that are subject to FDA jurisdiction.

33. One comment stated that proposed § 56.3(l) could be read to require that there must be a therapeutic benefit for all subjects who participate in an investigation and thus to eliminate all Phase I studies. The comment asked that this confusion be clarified.

The revised definition of "human subject" § 56.102(e) establishes that no therapeutic benefit for the participant from the research is required. The revision clarifies that these regulations do not eliminate Phase I studies.

34. One comment suggested that the proposed definition of "subject" be used in all regulations and guidelines dealing with clinical investigations.

Whenever possible, FDA has tried to use consistent definitions in each of its bioresearch monitoring regulations.

35. One comment stated that a definition of "informed consent" is needed in Part 56. FDA does not believe that the concept of informed consent can be adequately defined in a single "definition." Because the concept of informed consent is complex and should apply to any clinical investigation, FDA is publishing its provisions concerning informed consent separately in Part 50 to apply to all aspects of biomedical research in human subjects.

36. Several comments pointed out that an investigator may not always conduct an investigation or provide immediate direction under which a test article is administered, even though the investigator does exercise a supervisory role. These comments suggested a number of modifications in the proposed definition of "investigator" in § 56.3(g) (now § 56.102(h)).

FDA recognizes that a single investigator does not always immediately direct the administration of the test article. Therefore, FDA has revised § 56.102(h) to reflect more accurately the functions of investigators.

37. Several comments stated that the proposed definition of "minimal risk" in § 56.3(h) (now § 56.102(i)) should be the same as the HHS definition. One comment stated that the proposed FDA definition was too narrow.

FDA agrees with the comments and has rewritten § 56.102(i) to match the revised HHS definition. The definition in these final regulations takes into account the fact that risks encountered in the daily lives of healthy individuals may not be the same as risks encountered in the daily lives of others, and that "minimal" risk should mean that no risk in addition to that already encountered in the daily life of the individual will arise from the study.

FDA points out to those IRB's and investigators involved with medical devices that the term "minimal risk" used in Part 56 is different from the term "non significant risk" that is used in the IDE regulations. "Non significant risk" is used to describe a medical device. "Minimal risk" is used to describe an investigation and involves different criteria from the ones used to determine that a device poses a "non significant risk." Thus, IRB's and investigators cannot assume that an investigation with a "non significant risk" device poses only a "minimal risk" for the purpose of Part 56.

38. One comment stated that cosmetics should not be included in proposed § 56.3(n), which defined "test article."

As stated in paragraph 19 of this preamble, cosmetics are excluded from the scope of the IRB regulations. The word "cosmetic" is deleted from § 56.102(1).

39. One comment stated that a definition of "substantial risk" is needed in the IRB regulations.

FDA disagrees with this comment. Having defined "minimal risk," there is no need to demarcate the levels of risk any further. All studies with greater than minimal risk are treated the same under these regulations.

40. Many comments on proposed § 56.5 (now § 56.103) objected to the requirement of IRB review of clinical investigations that are conducted outside of an institution.

Most of these comments overlap with or are identical to comments on § 56.101 *Scope*. The agency responded to these comments in paragraphs 15 through 18 of this preamble. The general objections will not be discussed further here.

41. Several comments on proposed § 56.5 stated that to require IRB review of studies involving non-institutionalized subjects will result in a tremendous additional burden on IRBs. One comment argued that, as a result of the regulations, it might become necessary for institutions to employ full-time reviewers, which would decrease the quality of persons serving on IRBs.

FDA disagrees with these comments. The agency does not expect that any existing IRBs will be overwhelmed with new studies. FDA has exempted all studies that begin before the effective date of these regulations from the requirement of IRB review (see § 56.104). Also, as discussed in paragraph 17 of this preamble, the agency anticipates that where the need arises to accommodate studies with non-institutionalized subjects, new IRBs will be formed by professional societies, local medical societies, etc.

42. One comment on proposed § 56.5 stated that IRBs formed to review research conducted by physicians in their private practices will pose a large problem because sponsors will be reluctant to deal with them out of fear that the IRBs will not properly review studies under these regulations, and, as a result, FDA will refuse to accept studies that the IRBs review.

FDA rejects this comment. The agency has made every effort to make these regulations as clear and precise as possible. The agency stands ready to answer any question an IRB may have abour these regulations. Consequently, there should be no reason for an IRB to be seriously out of compliance with Part 56. FDA emphasizes that the agency expects it to be a rare occurrence for studies reviewed by an IRB to be rejected because of the IRB's noncompliance with these regulations. This expectation is discussed further in paragraph 46 of this preamble.

43. Another comment on proposed § 56.5 suggested that device manufacturers should be allowed to set up IRBs to review protocols and patient consent forms for use by individual clinical investigators.

FDA agrees and points out that these regulations allow any manufacturer to set up an IRB. The agency advises, however, that one of the primary responsibilities of an IRB is to be sensitive to the concerns of the community in which the study will be conducted. Therefore, an IRB formed by a manufacturer or a sponsor must be aware of, and give full consideration to, those concerns.

44. Two comments stated that provision should be made in the final regulations for FDA to accept studies without IRB review where no IRB exists.

FDA rejects these comments. All human subjects of FDA regulated research (except for human subjects of the research specifically exempted by § 56.104 or for which a waiver has been granted under § 56.105 of these regulations) are entitled to the protection of IRB review. FDA is not willing to permit human subjects to be deprived of this protection simply because an IRB is not available locally. Although local review is preferable, FDA has never established local review as a rigid requirement. If an IRB is not available locally, review can be sought at an IRB established in any of the ways discussed in paragraphs 17 and 41 of this preamble.

45. A number of comments objected to proposed § 56.5(a) (now § 56.103(a)) because of the requirement that an application for a research permit must be reviewed and approved by an IRB before it could be accepted by FDA. One comment stated that it was wasteful to require IRB review of a study when FDA may later reject the application. Several comments stated that IRB review should take place after FDA has given its approval or, at a minimum, be concurrent with FDA review.

The agency has considered these comments and has modified § 56.103(a) to respond to the concerns. IRB review and approval will be required before any human subjects may enter into a clinical investigation. However, the IRB may review the study before, during, or after FDA conducts its review.

46. Two comments on proposed § 56.5(b) (now § 56.103(b)) suggested that data from a clinical investigation that were not subject to initial review by an IRB might be acceptable despite the absence of a review. One comment argued that if the agency does not

consider the data, it might deprive members of the public of the opportunity to use a test device that will benefit them. This comment suggested that the problem could be dealt with by permitting an investigation to be approved by an IRB after the fact.

FDA rejects these comments. Post hoc review by an IRB is contrary to the purposes of IRB review. FDA believes it possesses the statutory authority to reject the data from a study, even though the scientific validity of the data generated may not have been affected, when the clinical investigation did not receive IRB review, or when the clinical investigation was under the review of a disqualified IRB or was conducted at a disqualified institution. Although the agency may not reject the data in every case, it reserves the right to do so when circumstances so warrant, and § 56.103(b) has been modified accordingly. The agency will consider, among other factors, the risks to human subjects that would be created if it rejected the data and required that the study be redone.

47. One comment stated that FDA should not require IRB approval for studies being conducted after premarket approval of a regulated article has been granted by the agency.

The comment misunderstands the scope of these regulations, as stated in § 56.101. These regulations govern studies of regulated articles that are conducted for submission to FDA. Studies that are not intended to be submitted in support of an initial or supplemental research or marketing permit do not fall within the purview of these regulations. The agency believes, however, that the best protection for human subjects would be for all clinical studies to be reviewed by an IRB.

48. Many comments objected to the provision in proposed § 56.6 that would have waived the requirement for IRB review of clinical investigations begun prior to the effective date of these regulations only if those studies were completed within 1 year of the effective date. Some comments suggested that studies should be exempted if they were completed within 2 years. Others suggested that studies be exempted if completed within 3 years. Ten comments urged that the regulations should apply only to studies begun after the effective date.

FDA has decided to exempt all studies that were begun before the effective date of these regulations and that were not otherwise subject to a requirement of IRB review under FDA regulations before that date, and § 56.104(b) so provides. The agency believes that the administrative burden that would be created by requiring IRB review of studies that were begun before the effective date of Part 56 far outweighs any benefits to human subjects that might be created. If the requirement was extended, the large number of studies that IRBs would suddenly have to review would prevent them from reviewing new proposals and from undertaking their continuing review of previously approved research. FDA believes that IRBs should be free to concentrate on the latter two types of research.

However, FDA advises that any expansion of a study that would otherwise be exempt under § 56.104 (a) or (b) to include a new institution will be subject to IRB review. Thus, if a new institution is added to a multicentered study of an investigational drug or device after the effective date of these regulations, IRB review must be conducted at the new institution.

49. FDA received numerous comments about proposed § 56.6(b), which would have established the circumstances in which the requirement of IRB review could be waived. Several comments objected to this provision on the ground that human subjects would not be adequately protected if a waiver were granted.

FDA is in substantial agreement with the latter comments. However, the agency recognizes that there may be circumstances in which a waiver would be appropriate. Therefore, FDA has revised the waiver provision (§ 56.105) to provide a sponsor or a sponsor-investigator with an opportunity to request that the agency waive some or all of the IRB requirements. A waiver may be granted by the responsible Bureau. The agency cautions, however, that it anticipates using the waiver provision only in special circumstances, upon a showing that a waiver is in the interest of patients who are subjects, and that an alternate mechanism for assuring the protection of human subjects is available. FDA also advises that, at the present time, it will consider applications for a waiver for those investigational new drug applications that have been commonly termed "compassionate INDs" or "treatment INDs" or for the distribution of investigational drugs under an investigational new drug exemption for the treatment of patients when alternate therapy is not available or is less effective. FDA also points out that because the statute requires IRB review of device studies, the agency will not waive the requirement of IRB review in those cases.

50. One comment suggested that the FDA regulations concerning membership of an IRB should be identical to the HHS regulations.

FDA agrees, and the agency has rewritten proposed §§ 56.21, 56.25, 56.26, and 56.34 (now § 56.107) to conform to the revised HHS requirements.

51. Several comments stated that FDA should not require racial and cultural diversity of IRB members because this requirement may be inappropriate to the community that the IRB serves, and because this requirement has no relevance to the competence of persons who serve on an IRB. One comment stated that the IRB regulations are an inappropriate place to implement affirmative action plans.

These comments misinterpret § 56.107(a). The regulation does not require racial and cultural diversity in all cases. It requires that the racial and cultural backgrounds of the members be sufficiently diverse to assure that the IRB will be sensitive to the attitudes and concerns of the community and to the human subject population.

52. One comment suggested that it would be helpful if the term "cultural background" was defined.

FDA has used the term "cultural background" in § 56.107(a) to encompass such socio-economic characteristics as age, economic status, and ethnic origin.

53. One comment suggested that provision be made in the regulations for an IRB to include alternate members.

Although § 56.107(a) does not explicitly provide for alternate members, it would allow an IRB to adopt written procedures (see § 56.108) for using alternate members in the IRB's deliberations in case one of the regular members is absent or is disqualified from considering a proposal because of a conflict of interest. FDA points out, however, that the names of any alternate members must be included on the list of IRB members required by § 56.115(a)(5).

54. Several comments stated that there was no basis for requiring an IRB to have members of both sexes. Two comments suggested that a balance of men and women might not always be possible, and therefore, the requirement should be amended to read, "if possible."

FDA rejects these comments. The agency believes that to achieve a reasonable ethical perspective, IRB membership should be comprised of both men and women. Section 56.107(b) does not require that the number of men and women be equal. Rather, it requires that the IRB not be made up only of men or only of women. FDA points out that this requirement does not mean that members of both sexes are required to

be present for a quorum. No comments pointed to any specific situations in which it would not be possible to find competent men and competent women to serve on an IRB.

55. Several comments stated that the standards for IRB membership in the proposed regulations were too restrictive. The comments urged that FDA adopt more flexibile requirements on the make-up of an IRB. Three comments pointed out that it would not always be appropriate to have a physician or to have a scientist on a five-member board. In contrast, one comment stated that the proposed requirements for IRB composition were too vague.

FDA recognizes that it cannot specify in detail the composition of an IRB that would be appropriated to review each of the diverse types of studies that are included within FDA jurisdiction. Therefore, FDA has rewritten § 56.107 to allow an institution great flexibility in the make-up of its IRB. The regulation sets forth the minimum requirements that FDA believes must be met if an IRB's advice and counsel are to receive respect. In addition to the racial and cultural diversity discussed in paragraph 51 of this preamble, an IRB must possess the professional competence to review the research activities it considers (§ 56.107(a)). It may not be made up of members of one profession (§ 56.107(b)). An IRB must include at least one member whose primary concerns are in nonscientific areas (§ 56.107(c)), and at least one member must have no connection to the institution except for his or her membership on the IRB (§ 56.107(d)). FDA has eliminated the requirement that an IRB must include at least one physician and one scientist in all cases. This change was made in consultation with HHS to achieve identifical requirements and takes into consideration the need for some flexibility in the make-up of IRBs that review FDA-regulated research. However, FDA emphasizes that § 56.107(a) requires that IRBs have as members persons with the professional competence necessary to review the proposed research. For example, FDA would expect that an IRB that reviews investigational new drug studies will include at least one physician.

56. One comment suggested that it would be helpful if the term "nonscientist" was defined.

FDA believes that the examples given in § 56.107(c) of the types of individuals "whose primary concerns are in nonscientific areas" adequately explain this term.

57. One comment stated that in spite of the recommendation of the National Commission that an IRB that regularly reviews research that has an impact on vulnerable subjects should include persons who are primarily concerned with the welfare of those subjects, no provision for special representation of vulnerable subjects was contained in the proposed regulations.

FDA disagrees with this comment. Such a requirement is contained in § 56.107(a).

58. One comment recommended that rather than setting out a specific number of lay persons to serve on an IRB, the regulation should establish a minimum proportion of the membership that is to be nonscientists.

FDA disagrees with the comment. The standards set forth in these regulations are minimum standards that must be met by an IRB. If an institution or IRB wishes to exceed these standards and have a certain proportion of the IRB members be nonscientists, it is free to do so. However, an IRB must retain the necessary expertise to effectively review any protocol submitted to it, and therefore, it may need a number of scientists (whether medical doctors, dentists, technical staff, or others) on the IRB. FDA believes that, except for minimum standards, it should not dictate how many people should be from a specific profession.

59. One comment objected to the exclusion from membership on an IRB of immediate family members of a person affiliated with the institution. This comment stated this requirement would put severe restraints on recruiting IRB members in academic communities.

FDA points out that § 56.107(d) does not exclude members of the immediate family of a person affiliated with an institution from being members of an IRB. However, none of those family members may serve as the nonaffiliated member of the IRB. This rule is consistent with the National Commission's recommendation. FDA believes that even in small academic communities in IRB can find at least one person willing to serve on the IRB who is not affiliated with the institution and who is not the immediate family member of a person affiliated with the institution.

60. Many comments stated that under proposed § 56.26 (now § 56.107(e)), members of an IRB who selected other members would be precluded from conducting research. Several comments stated that the requirement should only be that an IRB member may not participate in the IRB's initial or continuing review of a clinical investigation in which the member has a conflicting interest. One comment suggested that the section should be modified so that no investigator would select IRB members solely to review his or her own investigation. One comment stated that IRBs at larger institutions had sufficient numbers of members to permit members to disqualify themselves if they felt there was a conflict of interest.

FDA agrees that revision is needed and has rewritten § 56.107(e) to coincide with the corresponding section in the Department's regulations. This requirement now provides that no member of an IRB may participate in the IRB's initial or continuing review of any clinical investigation in which the member has a conflicting interest. FDA believes that the IRB or the institution should determine what constitutes a conflicting interest.

61. One comment suggested that for each local IRB to seek consultative opinions on studies proposed for many research centers is redundant and would hinder the timely initiation of important research.

FDA agrees with this comment. Cooperative review of multi-institutional studies is expressly authorized by § 56.114. Expert technical opinion can be provided by a central source, so that each IRB can use that opinion to evaluate the study in light of the ethical standards of the local community.

62. One comment on proposed § 56.34 (now § 56.107(f)) suggested that consultants be allowed to vote with an IRB.

FDA rejects this comment. The decision of an IRB must represent the judgment of the members of the IRB. Although consultants should provide information about the ethical acceptability of a study, FDA believes it would be a distortion of their function to permit them to vote. Therefore, § 56.107(f) prohibits consultants from voting.

63. One comment on proposed § 56.80 Now § 56.108(a)) suggested that the requirement in the 1978 proposal that an IRB adopt written procedures for the initial and continuing review and monitoring of clinical investigations be modified to delete the requirement of "Monitoring." The comment argued that the sponsor was primarily responsible for monitoring.

FDA deleted the term "monitoring" from reproposed § 56.80 in the August 14, 1979 document. FDA has further rewritten § 56.108(a) in these final regulations to match the HHS section. However, FDA points out that IRBs are responsible for the continuing review of a study to ensure that the rights and welfare of human subjects are protected. Therefore, FDA would expect IRBs to review studies at a frequency consistent

with the risks and to consider those data that bear on the rights and welfare of the human subjects. (See paragraph 69 below.)

64. One comment stated that instead of uniformity among IRBs, there will probably be diversity because each IRB will be able to establish its own regulations within the loose Federal framework.

FDA agrees that each IRB will be able to establish its own procedures within the Federal framework, which represents minimum standards. An institution or IRB is free to impose greater standards of protection for human subjects than those required by these regulations. As stated previously, FDA does not believe that it should provide detailed directions to IRBs on how they are to comply with these regulations. How the IRBs meet the general standards should be left to each individual IRB and institution.

65. A few comments stated that IRBs are being forced into a "police role" as opposed to an ethical review in an atmosphere of trust and cooperation.

FDA disagrees with the comments. There is no requirement that IRBs treat investigators with less cooperation than in the past. However, it is up to the IRB to assure itself, by whatever method it deems appropriate, and to assure FDA that the rights and welfare of human subjects are being protected. FDA encourages IRBs and clinical investigators to cooperate and interact with each other in a nonadversarial manner. Nevertheless, FDA considers it an appropriate requirement that IRBs develop procedures to determine whether there is a need for verification, from sources other than the investigators, that there has been no material change in certain protocols since their previous review. Verification is not required by FDA but should be an available avenue when, in the opinion of the IRB, verification will provide necessary protections for subjects involved in greater than minimal risk research.

66. Several comments on proposed § 56.81 objected to defining a quorum in terms of specific professional groups that must be represented. These comments asserted that such a requirement could have the effect of giving one member of the IRB the power to prevent the IRB from meeting by refusing to appear. A few comments suggested possible remedies to this situation, including adopting a rule that any member who missed two consecutive meetings of an IRB without good cause would automatically be dismissed.

As stated previously, FDA believes that, within the framework of these regulations, each institution or IRB should set up its own rules and procedures governing IRB membership and attendance. However, FDA believes that it is important that a person whose primary concerns are in nonscientific areas be present when the IRB conducts its business because that member represents an important element of diversity. Therefore, FDA has retained in § 56.108(b) the requirement that the nonscientific member must be present for there to be a quorum. To ensure that a nonscientific member will be present, an IRB may wish to have more than one member whose primary concerns are in nonscientific areas.

67. Several comments stated that FDA should allow meetings to take place by conference calls. These comments argued that effective dialogue can occur between IRB members on conference calls without forcing the members to be physically present in one room.

Although FDA, like HHS, encourages meetings to take place with members physically present in the room, FDA also recognizes that in some cases time and commuting expense would favor conference calls. As long as each IRB member can actively participate in any discussion of a protocol and has all pertinent material before the call, FDA has no objection to allowing meetings to occur in such a fashion and will consider meetings that take place by conference call to be "convened" meetings. These meetings must follow the same requirements (minutes, etc.) as meetings with members physically present.

68. One comment stated that the proposed requirement in § 56.87(b) (now § 56.108(c)) that an IRB report any serious or continuing noncompliance by investigators with the IRB's determinations to the institution and to FDA extends beyond the intended role of an IRB.

FDA rejects this comment. During the course of its continuing review of a study, an IRB may become aware that a clinical investigator has not complied with its requirements or determinations. If the noncompliance is serious enough, an IRB may withdraw its approval of the investigation. Disciplinary action against the investigator may also be in order. Consequently, FDA has required in § 56.108(c) that the IRB report an investigator's serious noncompliance to the bodies that have authority to take action against the investigator—the institution and FDA.

69. One comment on proposed § 56.87(b) agreed that it was appropriate for IRBs to report any noncompliance with the requirements of the IRB to FDA, but the comment stated that IRBs should also have authority to suspend the investigator until the situation is reviewed by FDA.

Under § 56.113, the IRB is authorized to suspend or terminate its approval of any research that is not being conducted in accordance with the IRB's requirements or that has resulted in unexpected serious harm to human subjects. Where appropriate, action against a clinical investigator may be taken by FDA, or by the institution either directly or through the IRB if that authority is delegated to the IRB by the institution.

70. One comment stated that it was unclear in proposed § 56.82 whether a complete review of a proposed investigation is necessary if minor changes in the protocol, requested by the IRB, are agreed to by the investigator and the sponsor.

FDA believes that it is up to each individual IRB to decide whether it wants to review the study completely or merely to note that the requested changes have been made. However, the IRB must maintain documentation of changes made (§ 56.115(a)(2)). FDA has rewritten § 56.109(a) to match the corresponding section in the Department's regulations. This section provides that the IRB shall review and shall have authority to approve, to require modifications in, or to disapprove all research within FDA's jurisdiction.

71. Many comments objected to proposed § 56.82(a) because they interpreted the proposed regulations to require IRBs to conduct a scientific review of pertinent prior animal and human studies with the test article, as well as ethical review. A few comments stated that IRBs may not wish to see the complete animal studies but may wish to see only the conclusions from those studies.

FDA has deleted the requirement of review of prior studies from § 56.109(a). FDA emphasizes that it would not expect an IRB to conduct a scientific review of a study except to the extent necessary for the IRB to assure itself that the human subjects will not be needlessly placed at risk. However, an IRB is free to review prior studies, in whole or through summaries.

72. On its own initiative, FDA has added § 56.109 (b) and (c) to these regulations to make explicit an IRB's obligations with regard to the informed consent materials that are to be given to human subjects by the investigator (see Part 50 published elsewhere in this issue of the **Federal Register**).

73. One comment suggested that FDA explicitly authorize IRBs to require that human subjects in studies involving greater than minimal risk be given a cooling off period in which to consider the information that they have been given as part of the informed consent process.

FDA does not agree that there is a need to make such an explicit authorization. Implicit in the IRB's authority to review the information given to human subjects as part of informed consent is the authority to require that a specific period of time must lapse between when the information is presented to a potential subject, and when the subject must decide whether to participate in the investigation.

74. One comment suggested that informed consent materials be sent to FDA for approval before the start of a study.

FDA disagrees with this suggestion. Because IRB review includes an assessment of the adequacy of informed consent, FDA does not believe that prior approval of informed consent materials by FDA is necessary for all of the clinical investigations submitted to the agency. However, FDA points out that it may review consent materials if they are submitted as part of an application for a research permit or during the course of an inspection of an IRB or clinical investigator.

75. Many comments objected to the requirement in the proposed regulations that the IRB notify the investigator or sponsor in writing that it has received the proposed investigation. A few comments stated that the actual paperwork used by an IRB to conduct its business is its own responsibility. Another comment, however, stated that both the investigator and the sponsor need to be informed of IRB activities, so both should be notified when the study is received for review.

FDA agrees that this requirement should be deleted from the final regulation. The decision of the IRB to approve or not to approve the study, rather than the date of receipt of the study for review, is the information that must be communicated to the investigator (see § 56.109(d)).

76. Several comments suggested that an IRB has no relationship to the sponsor but only to the investigator and the institution. These comments suggested that, consequently, an IRB should not have to communicate at all with the sponsor.

As explained in paragraph 5 of this preamble, FDA agrees with these comments and has deleted from § 56.109(d) the requirement that the IRB notify the sponsor.

77. Several comments objected to the requirement contained in the proposed regulations that an IRB must approve or disapprove an investigation as soon as possible after receipt of the proposal. These comments suggested that this requirement could be interpreted to mandate that special meetings be convened merely because a study was submitted or could lead to confusion about what "as soon as possible" meant.

FDA agrees with these comments and has deleted this requirement from the final regulations.

78. One comment on proposed § 56.87 (now § 56.109(c)) stated that it was unclear how often an IRB should review research covered by these regulations.

Section 56.109(c) explicitly states that review shall occur at intervals appropriate to the degree of risk but not less than once per year.

79. Several comments stated that in the provisions for continuing review of research by an IRB, FDA is attempting to delegate its authority to enforce the act to a group of private citizens. One comment stated that this provision would make the IRB into an investigator for FDA. These comments stated that the act does not grant FDA authority to make such a delegation.

FDA rejects these comments. FDA is not delegating its authority to enforce the act. However, unanticipated risks are sometimes discovered during the course of an investigation, and new information sometimes comes to light showing that the risks in a study are not justified. Periodic review will assure that these risks are promptly brought to the IRB's attention and will provide extra protection to subjects. Consequently, FDA believes periodic review by an IRB is essential if an IRB is to adequately protect the rights and welfare of the human subjects involved in a clinical investigation. In paragraph 4 of this preamble, FDA already discussed its authority to adopt requirements that protect human subjects and there is no need to repeat that discussion here.

80. One comment suggested that these regulations should authorize IRBs to require investigators to provide human subjects with any new knowledge about a test article that is developed during the course of a study.

FDA and HHS have both provided as an additional element of informed consent that significant new findings developed during the course of the research that may affect the human subject's willingness to continue to participate must be provided to the subjects. Section 50.25(b)(5) of FDA's informed consent regulations published elsewhere in this issue of the **Federal Register** so provides for investigations that fall within the jurisdiction of FDA. The comment does not require any change in Part 56.

81. Several comments on proposed § 56.83 (now § 56.110) offered suggestions of different types of studies that should receive expedited review.

FDA has carefully reviewed these comments, along with the comments on expedited review received by HHS, and has developed a list of procedures that, if they involve no more than minimal risk, can receive expedited review. Publication of the list is provided for in new § 56.110. FDA had decided that expedited review should play a much more important role under the final regulations then the agency originally proposed. After reviewing the comments, FDA believes that it is unnecessary to require that a full IRB meet to consider every study. For studies that present minimal risk, expedited review strikes the appropriate balance between protection of patient and minimizing the burdens imposed by these regulations.

The expedited review list has been separated from the text of these regulations and is published as a notice elsewhere in this issue of the **Federal Register**. FDA views this list as being subject to change and encourages public comment on what additional classes of research should be included in this list. The agency will publish appropriate revisions of the list in the **Federal Register** as the need arises. FDA also points out that the Department is publishing a slightly different list, but the differences are caused by the fact that HHS funds many types of studies that do not fall within FDA jurisdiction.

82. One comment on proposed § 56.83 suggested that because some changes in protocol are universally accepted as minor, they should be listed in the regulations. Another comment suggested that "minor change" should be specified to avoid confusion.

FDA disagrees with these suggestions. The scope of investigations regulated by FDA is so broad that FDA does not believe that it is feasible for the agency to list all of the different changes that might be considered to be minor. The agency advises that it considers that changes that result in increased risk to human subjects are not minor. However, FDA is unable to generalize about whether changes that apparently do not entail increased risk are minor. For example, the agency recognizes that a substantial increase in the number of human subjects above that originally approved by the IRB might be

considered to be a minor change in some clinical studies but a major change in others. Therefore, FDA believes that it is up to the IRB to determine on a case-by-case basis whether a proposed change in a protocol is minor. The agency intends to provide additional guidance on this issue in the educational program that it will conduct with the Department. The comments are rejected.

83. On its own initiative, FDA has added new § 56.110(c), which matches the HHS requirement, so that all members of an IRB will be kept informed of the studies approved under the expedited review procedure. FDA believes that it is important that all IRB members know what studies are being approved at that institution. An IRB is free to adopt specific procedures for keeping individual members informed.

New § 56.110(d), which is also identical to the HHS provision, permits FDA to suspend an IRB's use of expedited review when it becomes necessary to protect the rights or welfare of the human subjects involved in a study. Although it is unlikely that this provision will be used by the agency except in the most unusual circumstances, FDA believes that it is important, to protect human subjects, to retain this flexibility in the regulation.

84. Several comments on proposed § 56.86(a) (now § 56.111(a)(1)) objected to IRB review of research methods, stating that IRBs are not qualified to conduct such review, and that IRB's primary responsibility is not to determine the scientific merit of the study.

FDA agrees with these comments. It has drafted § 56.111(a)(1) to focus on the risks to subjects. FDA reemphasizes that IRBs need not conduct scientific reviews of clinical investigations except to the extent necessary to determine that human subjects will not be exposed unnecessarily to risk.

85. One comment on proposed § 56.86(c) asserted that the meaning of the phrase "safest procedures" is unclear.

FDA agrees and has revised § 56.111(a)(1)(i) to clarify the intent of the regulations with respect to risk.

86. One comment suggested that FDA adopt the HHS language on use of procedures being performed for diagnostic or treatment purposes, when these procedures are appropriate.

FDA agrees with the comment and has adopted language in § 56.111(a)(1)(ii) to match the HHS requirement. The IRB should ensure that if procedures that are to be used in a study are already being used on a human subject for diagnostic or treatment purposes, the research procedures will be coordinated with the diagnostic or treatment procedures to avoid unnecessary repetition of the procedures.

87. Two comments suggested that proposed § 56.86(d) requiring that "risks to subjects be reasonable" and that "the importance of the knowledge to be gained should be considered" needed clarification.

FDA has rewritten § 56.111(a)(2) to match the HHS requirement. FDA advises that in a placebo-controlled trial, for example, no immediate benefit to the placebo group would be anticipated, so that the risks to that group must be reasonable in relation to the importance of the knowledge to be gained in the research. The regulations now state that the IRB shall not consider possible long-range effects of the knowledge gained in the research as a risk of conducting the research. Only those risks that relate to the particular human subjects involved in the investigation must be considered by the IRB.

88. Two comments on proposed § 56.86(b) (now § 56.111(a)(3)) stated that the term "equitable" was ambiguous and needed further explanation.

FDA disagrees with the comments. Special subgroups of the population should not have to bear a disproportionate amount of the risks of research that benefits others. The subjects of an investigation should not come from any particular group simply because it is convenient for the investigator to draw from that group. Scientific design and alternate human subject populations should be considered in assessing whether the selection of subjects is "equitable." For example, the IRB should require that the investigator justify the proposed involvement in the study of hospitalized patients, of other institutionalized persons, or of disproportionate numbers of racial or ethnic minorities or persons of low socioeconomic status. The comments are rejected, and § 56.111(a)(3) is published as proposed.

89. One comment questioned the meaning of the requirement in proposed § 56.86(g) (now § 56.111(a)(6)) that, where appropriate, data be monitored.

Where appropriate, IRB's should require that the research plan make adequate provision for monitoring the data collected to ensure the safety of human subjects. This procedure might be an appropriate requirement in large scale clinical trials or in studies with a high degree of risk. The IRB may require the use of data safety monitoring boards in order to meet the requirements of this provision. Thus, if it becomes clear that risks are greater than anticipated, or that the benefits do not justify the risks of the research, the IRB is informed and can act on the information. This provision matches the HHS requirement.

90. One comment suggested that each IRB should set out guidelines for determining at what point in each experiment one treatment is shown to be safer and more effective than alternate treatments or no treatment.

FDA disagrees with this suggestion. IRBs generally will not have the scientific consistence to make such a judgment. The determination whether and at what point in an investigation a test article has been shown to be safe and effective in accordance with the requirements of the act is a determination that must be made by the investigator, the sponsor, and, ultimately, FDA. The comment does not require any change in the regulations.

91. One comment stated that the regulations should protect vulnerable groups, such as minorities. The comment stated that neither the HHS nor the FDA proposed requirement was sufficient in this regard.

FDA has rewritten § 56.111(b) (and HHS has rewritten the corresponding provision in its regulations) to require that the IRB assure that appropriate additional protections are provided if the human subjects are from a vulnerable group.

92. One comment stated that before exposing human subjects to risk, an IRB should be required to make a determination that treatment is available for injuries that may arise from the research.

FDA disagrees in part with this comment. Section 50.25(a)(6) of the informed consent regulations requires that the subject be told if treatment for injuries is available. It should then be up to the subject to decide if he or she wishes to participate in the study. However, FDA agrees that the IRB should determine whether the investigator has made adequate provision for emergency medical care, if it appears that such emergency care may become necessary during the course of the investigation.

93. One comment suggested that IRB's should follow human subjects after completion of the study, unless the investigator can show that it is not necessary to do so.

FDA disagrees and rejects the suggestion. If anyone should follow subjects after completion of the study, it is the investigator or the sponsor. IRBs are generally not in a position to follow human subjects. If an IRB believes that it is necessary to do so to protect the subjects, it can require as part of the

protocol that the investigator follow subjects after the completion of the study.

94. Several comments on proposed § 56.8 stated that a means is needed for an investigator, a sponsor, or an institution to appeal an IRB ruling.

FDA has renumbered § 56.8 as § 56.112 in the final regulations to conform with those issued by HHS. The National Commission did not recommend that there be a mechanism for appeal from IRB determinations. However, there is nothing in § 56.112 that would prevent an institution from formulating an appeals mechanism, so long as the final ruling body is an IRB that satisfies the requirements of Part 56. Appeal of an adverse IRB determination to other institutional bodies that do not meet the requirements of Part 56 is not allowed under the regulation.

95. One comment questioned why officials at an institution could overrule IRB approval but not IRB disapproval of a study. Another comment stated that § 56.8 might abrogate the authority of the head of and institution.

Review and approval of a proposed clinical investigation by an IRB should not preclude a subsequent decision by the institution itself to reject the investigation. Officials of the institution take into account factors other than ethical acceptability and patient protection in deciding whether to authorize a particular investigation. For example, IRBs do not make decisions regarding the priority of funding studies or policy on whether to conduct a certain type of study at the institution. Therefore, FDA believes that institutional officials should have the authority to overrule an IRB's decision to approve a study. At the same time, FDA has decided not to authorize an institution to overrule and IRB's rejection of a study. If an institution had that authority, and IRB would become merely advisory, and its responsibilities would be eliminated. The comments do not warrant any change in the regulations.

96. Several comments on proposed § 56.92 stated that the sponsor should be given notice of a decision by an IRB either to suspend or to terminate approval of a clinical investigation.

FDA rejects these comments for the reasons explained in paragraphs 5 and 76 of this preamble.

97. One comment on proposed § 56.92 (now § 56.113) stated that once FDA has acted on an application for a research permit, it would be unfair to allow an IRB to suspend its approval of a particular clinical investigation.

FDA disagrees with the comment. An IRB focuses on different factors in its review of a proposed investigation than the agency considers in deciding whether to grant a research permit. Consequently, approval of a proposed investigation by either an IRB or FDA does not preclude the other entity from suspending or terminating the approval of the investigation at a later date.

98. FDA has deleted from the final regulations the criteria for disapproval and suspension or termination of approval of a clinical investigation that were proposed in § 56.90. Section 56.113 now states that an IRB may suspend or terminate its approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. This section now conforms to the HHS provision. The agency believes that the section, as revised, adequately specifies general criteria for the suspension or termination of the IRB's approval of an ongoing study. The section also requires that the IRB promptly notify FDA of its actions. Where necessary, FDA can, in turn, take any steps necessary to assure that the subjects are protected.

99. Several comments objected to the requirement in proposed § 56.90 that, after suspending or terminating approval of an investigation, the IRB make recommendations to FDA about the care of the human subjects of that investigation. The comments argued that it was the responsibility of a physician, and not an IRB, to make such recommendations.

FDA agrees with the comments and has deleted this requirement from the final regulations. The agency believes that this requirement inappropriately imposed medical responsibilities on an IRB. The responsibility for human subjects in a study for which IRB approval has been suspended or terminated is more properly shared by the clinical investigator, the institution, and the sponsor.

100. Section 56.114 in the final regulations was proposed as § 56.9. That section has been rewritten for clarity but there is no change in its intent. It is now consistent with the corresponding provision in the HHS regulations. The purpose of this section is to assure IRBs that FDA will accept reasonable methods of joint review. Thus, an IRB need not re-review a study that has already received approval from another IRB, unless it chooses to do so. However, FDA advises that the requirement for the IRB to be sensitive to such factors as community attitudes (§ 56.107(a)) is applicable to § 56.114. The IRB's records must include, either in the minutes or elsewhere, documentation of agreement that a specific study will be reviewed cooperatively.

101. Two comments on proposed § 56.185 (now § 56.115) suggested that the records of an IRB should be maintained by the institution rather than by the IRB.

FDA agrees that, in some cases, it may be more feasible for an institution to maintain the records of an IRB. Consequently, FDA has rewritten § 56.115(a) to provide that either the institution or the IRB may be responsible for preparing and maintaining adequate records of IRB activities.

102. One comment stated that it is unreasonable to require IRBs to keep records because they lack adequate storage facilities.

FDA advises that if an institution delegates the responsibility to maintain records to an IRB, it must also provide the IRB with adequate facilities to do so. The comment does not justify any change in § 56.115.

103. One comment suggested that proposed § 56.185 should spell out every record that the agency wants an IRB to keep. The comment stated that the proposed requirements were not sufficiently detailed.

FDA disagrees with this comment. Section 56.115(a) in the final regulations sets forth the minimum records that an institution or an IRB must keep to document the activities of the IRB. The IRB or the institution is free to maintain additional records if it chooses. However, FDA does not believe that any more extensive recordkeeping by the IRB or the institution is necessary.

104. Five comments objected that the documentation FDA proposed to require was an unnecessary burden on IRBs. These comments argued that the proposed documentation is not necessary to protect the rights and welfare of human subjects.

FDA rejects these comments. The agency believes that the records that an IRB or an institution must maintain under § 56.115(a) provide significant evidence of whether the procedures utilized by the IRB are adequately protecting the human subjects of the investigations that the IRB is reviewing. For example, when an IRB approves the use of a "short form," for informed consent as provided in § 50.27(b)(2), FDA would expect the IRB to retain in its files a copy of the written summary of the oral presentation of informed consent information that is given to human subjects in the clinical investigation.

105. Several comments stated that proposed § 56.185(d) (now § 56.115(a)(2)), which requires that the minutes of an IRB meeting include a summary of the discussion of substantive issues, is not reasonable.

FDA agrees in part with the comments. The National Commission recommended, and FDA agrees, that it is important to maintain detailed minutes of IRB meetings. However, FDA decided to reduce the burden on IRBs by requiring that the minutes contain: (1) A basis for IRB action only when the research is disapproved or requires modification; and (2) A written summary of the IRB discussion and resolution only when it involves controversial issues.

FDA does not believe that summarizing the discussions of controverted issues in the minutes will have a chilling effect on those discussions because FDA does not require the identification of specific individuals with specific comments in the summaries.

106. One comment suggested that minutes could be kept by an audio tape recording, which would be complete and more accurate than any summary.

FDA agrees that a tape recording is a more complete record of the meeting. However, FDA advises that retention of complete recordings of meetings does not relieve an IRB of its obligation under § 56.115(a)(2) to keep at least brief written summaries of its meetings that must be available for inspection.

107. A few comments stated that the voting records of individual members should not be kept. The comments stated that this requirement would have a chilling effect on IRB members.

FDA believes the requirement has been misunderstood. Proposed § 56.185 did not include such a requirement nor does § 56.115 of the final regulations. Section 56,115(a)(2) requires only that the number of members voting for and against a study be kept. While the members attending the meeting would also be recorded in the minutes, individual voting records are not required.

108. Three comments objected to any requirement that voting records be kept.

FDA disagrees with these comments. The voting records must be included in the IRB records for FDA to document that a majority of those members present voted in favor of conducting a particular study at that institution.

109. One comment suggested that individual voting records of IRB members should be submitted to FDA, so that even if a member objected to a study but was overruled by the other members, the objection would come to the attention of FDA. The agency could then take appropriate action.

FDA disagrees with this suggestion. Section 56.115(a)(2) already requires that votes of an IRB be recorded, and that any controverted items discussed be summarized in the minutes of IRB meetings. Consequently, there is no need to record individual members' voting records. In addition, except in the most extreme circumstances, FDA does not believe that it should second guess a properly constituted and well-functioning IRB on the ethical acceptability of a study.

110. Several comments objected that the records about the members of an IRB that were required in the proposed regulations were overly burdensome.

The recordkeeping requirements in § 56.115(a)(5) have been limited to provide that only information that necessarily bears on the IRB's impartiality and expertise must be maintained.

111. One comment stated that the record retention time required by proposed § 56.195 (now § 56.115(b)) disregarded the possibility that problems might not appear for 20 to 30 years.

This comment suggested that the regulations should be changed to require that records be kept 7 years for adults and 25 years for minors and pregnant women.

Although an institution is free to adopt a longer requirement, FDA has decided to match the HHS provision that records must be kept a minimum of 3 years. The agency believes that the 3-year requirement strikes an appropriate balance between the need to retain records and the administrative burdens involved. Although some problems may not become apparent for 20 years or more, those instances are so rare that the agency concludes that they do not justify an absolute requirement that all IRB records be retained for such an extended period of time. In addition, FDA reviews IRBs on a 2-year cycle. Thus, the 3-year requirement will ensure that all of the important records of the IRB will be available for FDA review. If, however, an institution or an IRB believes that in a particular study it would be appropriate to retain the IRB records longer to protect the human subjects involved, the institution or the IRB is of course free to do so.

112. One comment stated that the period that IRBs or institutions are required to retain records should be consistent with the record retention requirements in the proposed regulations regarding obligations of sponsors and monitors of clinical investigations and the proposed regulations regarding obligations of clinical investigators.

FDA rejects this comment. The records covered by these regulations are quite different than those that are proposed to be required under the sponsor-monitor and clinical investigator regulations. Therefore, the agency believes that the three sets of regulations need not be consistent on this point. The agency believes it is more appropriate to keep § 56.115(b) consistent with the corresponding provision in the HHS regulations. FDA believes that the 3-year period satisfies the needs of the agency while not imposing an unreasonable administrative burden on IRBs or their parent institutions.

113. A few comments suggested that records could be maintained by microfiche, microfilm, or other similar photographic method, if the records are properly verified as being accurate reproductions of the original records.

FDA agrees with these comments. There is nothing in these regulations that would prevent records from being reproduced and retained in this manner.

114. Many comments objected to the requirement in proposed § 56.15(a) that FDA be allowed to copy patient medical records during an IRB inspection. Most comments stated that IRBs do not have individual patient records. Other comments questioned whether FDA was requiring IRBs to obtain those records. Many comments stated that there were problems with confidentiality if IRBs were to obtain individual patient medical records and maintain them in the files for 5 years after completion of a clinical investigation to which the IRB records relate. Many comments stated that if this information is needed by the agency, it is available from either the sponsor or clinical investigator and should be obtained through proper legal channels from those persons.

In response to the comments, FDA has deleted from the final regulations any requirement that patient records be maintained by an IRB or that patient records be made available to FDA during an inspection of an IRB. If it becomes necessary for FDA to see the medical records of individual patients, adequate authority exists under the act for FDA to obtain those records from the clinical investigator or sponsor. Also, because IRBs would rarely have individual medical records, FDA wants to assure IRBs that there is no need to obtain individual patient records to comply with the requirements of § 56.115.

115. One comment suggested that IRBs do not have to submit to inspection by

FDA because inspections require warrants.

FDA rejects this comment and declines to change § 56.115(b) to respond to the comment. As discussed in the preamble to the 1978 proposal, FDA has authority to inspect an IRB, in many cases, without the IRB's permission. Under section 704(a) of the act (21 U.S.C. 374(a)), FDA may inspect establishments in which certain drugs or devices are processed or held and may examine research data that would be subject to reporting and inspection under sections 505(i) or (j), 507(d) or (g), 519, or 520(g) of the act. Under section 704(e) (21 U.S.C. 374(e)), FDA may inspect certain required records concerning devices. Thus, most sponsors and many investigators of investigational new drugs and investigational devices, and the institutions at which such studies are conducted, are subject to FDA inspection whether they consent or not.

FDA advises that if an IRB refuses to permit inspection, FDA may, under § 56.115(c), reject the studies conducted under review of that IRB from supporting an application for a research of marketing permit, or the agency may seek a warrant to inspect. However, there is no requirement that FDA obtain a warrant before inspection.

116. Two comments stated that inspections were too long, and that FDA should provide more detail about how inspections are to be conducted.

FDA has recently mailed an information sheet on the inspection process to the approximately 1,500 individuals, institutions, and organizations that have communicated with the agency previously about IRB's. FDA also sponsored a workshop on IRB compliance activities on November 7, 1980 (announced in the **Federal Register** of September 26, 1980; 45 FR 63929). The agency will distribute the transcript of the workshop to interested parties; will evaluate the workshop as well as written comments on it; and will then decide whether to make modifications in the current inspection program. The transcript and the information sheet are on file under Docket No. 80N–0399 in FDA's Dockets Management Branch (HFA–305), Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857. The transcript and any comments on it may be seen in that office between 9 a.m. and 4 p.m., Monday through Friday.

The comments do not require any change in the regulation.

117. A few comments on proposed § 56.15(b) (now § 56.115(c)) stated that FDA has no authority to refuse to consider a clinical investigation in support of an application for a research or marketing permit if the IRB refuses to allow inspection by FDA officials. Some of the comments stated that FDA should have the burden of showing that the validity of the study is adversely affected by the IRB's refusal to allow inspection.

As stated in the preamble to the 1978 proposal, if follows from the authority to issue regulations establishing standards for IRBs that FDA also has the authority to prescribe the terms on which it will accept data generated in a clinical investigation reviewed by an IRB. Therefore, the agency may refuse to consider data from a clinical investigation in support of an application for a research or marketing permit, unless the IRB that reviewed the investigation consents to an inspection by FDA.

The connection between an IRB's refusal to permit an inspection and the agency's refusal to consider data is clear. FDA is charged by statute with the obligation of ensuring the protection of the rights and welfare of the human subjects who participate in clincial investigations involving articles subject to sections 505(i), 507(d), and 520(g) of the act. In performance of that obligation, the agency has adopted these regulations requiring IRB review. However, FDA has a concomitant obligation to ensure that these regulations are observed. FDA must verify that IRBs are operating in accordance with these regulations, and it must have access to the IRBs and their records to do so. When an IRB refuses to permit FDA to inspect its records, FDA cannot verify that the IRB is properly constituted and operating correctly. Consequently, the agency cannot be assured that human subjects have been given the protection that the IRB mechanism is intended to afford, and it may be appropriate for the agency to refuse to accept the data from the studies that the IRB has reviewed.

However, FDA points out two additional facts: First, before rejecting the data from a clinical investigation, the agency will review each study to determine whether the risks created by requiring the study to be re-done outweigh the benefits of rejecting the data.

Second, FDA expects that it will be a very rare occurrence for an IRB to refuse to allow an inspection by FDA personnel. FDA has found that the vast majority of IRBs are cooperative at the time of inspection.

The comments do not justify any change in § 56.115(c) from the regulation as proposed.

118. A few comments stated that it is unfair for the agency to "punish" the sponsor of a study by refusing to accept the data from a study that was reviewed by an IRB that refused to allow FDA inspection.

FDA has already explained in paragraphs 46 and 117 above that it will not automatically reject data. FDA also points out that, with these regulations (see § 56.120 et seq.), the agency has available more direct administrative actions against institutions and IRBs for noncompliance. Thus, the agency may apply sanctions directly against the entity that refused inspection. However, there may be occasions when it would be appropriate for the agency to also refuse to accept data, and FDA has reserved that option.

119. FDA received numerous comments criticizing the provisions of Subpart K of the proposed regulations (now Subpart E) relating to the disqualification of IRB's.

In response, FDA has simplified and streamlined Subpart E of the final regulations. FDA has also shifted the focus of the administrative sanctions for noncompliance from the IRB to the institution. The agency recognizes that an IRB is created by and is responsible to the institution. Consequently, it is the duty of the institution to assure that its IRB meets the obligations imposed by Federal statute and regulations. FDA believes that when an IRB is found not to be in compliance with the regulations, and the institution to which the IRB is responsible does not take positive steps to correct the deficiencies, the appropriate response is to take action against the institution. However, there are exceptions to this rule. If an IRB is not directly responsible to a single institution, e.g., where an IRB reviews clinical investigations for more than one institution, and the IRB is found not to be in compliance with these regulations, FDA believes it would be appropriate to take action directly against the IRB. A second exception is the situation in which an IRB is one of several directly responsible to a single institution, e.g., where an IRB reviews certain kinds of clinical investigations at the institution, and where an IRB is found not to be in compliance with these regulations. FDA believes that it may not be appropriate to disqualify all the IRBs at the institution because one is out of compliance. Therefore, FDA will take action against the individual IRB, and not against the institution, when the institution has taken all appropriate steps within its power to correct the IRB's deficiencies, but the IRB remains out of compliance.

Section 56.120(c) reflects the agency's shift in focus to the institution. However, the regulation also provides that FDA

may take action against an IRB or a component of the parent institution if the agency determines that it is appropriate to do so under the facts of the particular case.

120. Several comments on proposed § 56.202(c) suggested that the lesser regulatory actions that were referred to in the proposed regulations should be listed.

FDA accepts these comments. Section 56.120(b) has been added to the final rule to set forth the lesser administrative actions that the agency may take if FDA finds deficiencies in the operation of an IRB and to describe the circumstances in which these lesser administrative actions may be used by the agency.

121. Two comments stated that notification of other Federal agencies of a possible IRB disqualification, as provided in the proposed regulations, would presume that IRB is guilty before it had an opportunity for a hearing and would make it difficult to recruit members.

FDA rejects these comments. In most instances, FDA will not advise other Federal or State agencies of deficiencies in the operation of an IRB, unless the agency decides to disqualify the IRB or its parent institution. However, in § 56.120(b)(4), the agency has reserved the right to do so if it finds serious deficiencies in the operation of an IRB during an inspection. In addition, FDA, as an agency of HHS, will share knowledge gained from inspections with other agencies within the Department, including the National Institutes of Health.

122. A few comments stated that FDA should exhaust all other remedies before disqualification. Other comments suggested that the IRB should have an opportunity to correct or refute the deficiencies found by FDA.

Section 56.121(a) of the final regulations provides that disqualification proceedings will not be instituted by the agency, unless the agency determines that grounds for holding a hearing exist, and the institution or the IRB has failed to take adequate steps to correct the deficiencies listed in the letter sent by the agency under § 56.120(a).

123. One comment stated that if FDA decided to retain the disqualification mechanism, the regulations should clearly state that disqualification will be used only in the most extreme cases and not on a routine basis.

FDA agrees with this comment. Disqualification will be used by the agency only when it is necessary to protect the rights and welfare of human subjects, and after the institution or IRB has refused or has continuously failed to comply with these regulations. FDA hopes never to use this sanction, and, based on the demonstrated willingness of institutions to correct deficiencies in their IRBs, the agency does not expect to use this sanction except in the most extraordinary circumstances. However, the agency believes that it is important to retain the option to disqualify an institution or an IRB if it becomes necessary to do so to protect human subjects.

124. Several comments pointed out that nowhere in the act is disqualification mentioned. These comments consequently concluded that FDA lacks the authority to disqualify IRBs.

FDA disagrees and rejects these comments. FDA has previously discussed its authority to promulgate these regulations (see paragraphs 4 and 117 of this preamble). Inherent in that authority is the authority to enforce these regulations. Disqualification is an essential element of the enforcement mechanism adopted by the agency. Without such an enforcement mechanism, compliance with these regulations would be voluntary, and these regulations would be nothing more than guidelines that would not adequately protect human subjects.

125. A few comments suggested that disqualification of an IRB or an institution would only hurt the sponsor, because studies reviewed by the IRB would not be accepted by FDA. The comments stated that sponsors exert little control over IRBs and have little opportunity to ensure that IRBs comply with these regulations.

FDA believes that it has responded to these concerns in paragraph 118 of this preamble. FDA would suggest that a sponsor assure itself, through the clinical investigator, that the IRB that reviews the clinical investigation protocol meets FDA requirements.

126. Several comments suggested that FDA should send notice of the initiation of proceedings to disqualify an IRB or its parent institution to all investigators and sponsors whose studies are under the review of the IRB.

FDA rejects this suggestion. FDA believes it would be an unreasonable expenditure of agency resources for it to send out such notices prior to a hearing. While a great deal of effort would have to be expended in putting together a list of sponsors and investigators involved with the institution and in sending them notices, the reason for the notice could be easily mooted if the IRB comes into compliance, or if FDA decides against disqualification. The agency believes that its resources are better spent after the hearing, notifying all interested parties it can identify that the agency has decided to disqualify the institution or the IRB. FDA advises that this notification may require publication of the disqualification decision in the **Federal Register.**

127. One comment suggested that an additional provision should be inserted into the final regulations to allow the IRB 30 to 60 days to prepare for the hearing, except where the safety of the human subjects requires immediate action.

FDA rejects this suggestion. Hearings under these regulations will be conducted in accordance with the requirements for a regulatory hearing before the FDA set forth in 21 CFR Part 16. Adequate time to prepare for a regulatory hearing is afforded under those regulations.

128. Several comments objected to the grounds for disqualification set forth in proposed § 56.202 (now § 56.121(b)). One comment argued that a blanket statement that disqualification could be based on a failure to comply with any regulations regarding IRBs would open the door to harassment and abuse of this system. Two comments stated that although it would be appropriate to disqualify an IRB if its noncompliance adversely affected the rights and safety of human subjects, it made no sense to disqualify an IRB because its noncompliance affected the validity of a study.

FDA has revised the grounds in § 56.121(b) for disqualification. To assure that the remedy is invoked only when appropriate, § 56.121(b)(1) provides that an IRB's failure to comply must be repeated to be grounds for disqualification (see paragraph 129). Noncompliance that adversely affects the validity of an investigation is no longer a basis for disqualification (§ 56.121(b)(2)).

129. Two comments stated that failure to comply with these regulations should not trigger disqualification. One of these comments stated that FDA should have to show a willful intent not to comply.

FDA disagrees with these comments. Although disqualification will not be used lightly, the agency should not have to show that the IRB or the institution did not intend to comply with the regulations. Repeated failure to comply may or may not indicate a willful intent, but it is sufficient to trigger disqualification. Section 56.121(b)(1) of the final regulations so provides. The important point is that the failure to comply is repeated and not an isolated event. Of course, a flat refusal to comply with these regulations could also trigger disqualification.

130. Three comments stated that the regulations should provide that the agency will advise a sponsor of the disqualification of an IRB that is reviewing studies of that sponsor.

FDA accepts this comment and has revised § 56.121(c) to so provide. The agency will notify any sponsor of which it is aware that has had studies reviewed by the disqualified IRB. This notification may require publication of the disqualification decision in the Federal Register.

131. Several comments questioned whether an institution has to replace its IRB after the IRB is disqualified.

Because FDA has shifted the focus of these regulations from the IRB to the institution, disqualification will usually be directed at the institution itself. In order for the IRB of a disqualified institution to be in compliance with these regulations, the institution would have to be reinstated. The situation is somewhat different for institutions with more than one IRB or for institutions whose studies are reviewed by an IRB that serves several institutions. As discussed in paragraph 119 above, FDA may disqualify the IRB rather than the institution in such situations. Those institutions are then free to establish a new IRB, to replace the disqualified IRB, but FDA would not require them to do so. An institution with several IRBs may choose to have another IRB that is competent to assume the responsibilities of the disqualified IRB. For example, the institution would assign an IRB that normally reviews drug studies the responsibility to assume the review of drug studies that were previously under the review of a disqualified IRB. However, FDA would find unacceptable the assignment of those duties to an IRB that normally reviews behavioral research, whose members lack the professional competence necessary to review drug studies.

132. Several comments stated that investigations reviewed by an IRB before disqualification should not automatically be presumed to be unacceptable. A few stated that only the particular studies where deficiencies were found should be unacceptable to FDA.

FDA disagrees in part with the comments. FDA believes that if it is necessary to disqualify an institution or an IRB, the agency cannot be assured that any study conducted at that institution or reviewed by that IRB provided for the rights and welfare of the human subjects. Because disqualification will not be undertaken lightly, the deficiencies that required disqualification are likely to be so pervasive that they had an effect on more than one study. Therefore, FDA believes that any study reviewed by a disqualified IRB or conducted at a disqualified institution is suspect. However, as stated previously in paragraph 46 of this preamble, the agency will review the studies conducted as a disqualified institution or reviewed by a disqualified IRB to decide on a case-by-case basis whether to reject the data.

133. One comment expressed concern that confidential information would be disclosed to the public during the disqualification process. A few comments stated that no data, clinical reports, or records regarding particular studies ought to be disclosed.

Section 56.122 provides that the determination of the agency to disqualify an institution and the administrative record regarding that determination are disclosable to the public under the agency's public information regulations. Under § 20.61 (21 CFR 20.61), any trade secret or confidential commercial information in the administrative record is exempt from disclosure. Under § 20.63, medical and similar files, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy, are also exempt. Therefore, there is no basis for concern that confidential information will be disclosed, and the comments are rejected.

134. One comment stated that adverse publicity caused by disqualification would make recruitment for IRBs very difficult.

FDA recognizes that some adverse publicity may arise from a disqualification of an IRB or an institution. However, because IRBs play such an important role in the protection of human subjects, and because disqualification will be undertaken only when there has been a serious disregard by an IRB or an institution of its responsibilities, FDA believes it is appropriate to retain the disqualification mechanism and the provisions allowing the agency to publicly disclose the fact of the disqualification at the discretion of the agency.

135. One comment stated that because an IRB is created to serve an institution, any disqualification should be of the institution, and the burden of reinstatement should be placed upon that institution.

FDA generally agrees with these comments and, except for the situations discussed in paragraph 119 of this preamble, has changed the focus of disqualification and reinstatement to the institution. To be reinstated pursuant to § 56.123, an institution must adequately demonstrate to FDA how the concerned IRB will comply with these regulations. FDA does not believe that it should spell out exactly how the institution should demonstrate how compliance with these regulations will be assured, because institutions may choose different methods of assuring such compliance.

136. Three comments stated that additional sanctions against individual members of an IRB would make it difficult to recruit members to serve on any IRB.

FDA disagrees with these comments. Other sanctions will be used in cases where disqualification of the institution or the IRB might not be the appropriate action, e.g., where individual members of an IRB submit false information to the Federal Government, which is a criminal offense. The agency does not believe that qualified people will be deterred from serving on an IRB by the fact that they will be held accountable if they break the law.

137. One comment stated that in light of the other sanctions referred to in proposed § 56.215 (now § 56.124) disqualifications would be superfluous.

FDA disagrees with this comment. As stated in paragraph 123 of this preamble, while FDA expects to use disqualification only rarely, it is important that the agency retain the option to use it if the need arises. In some situations, disqualification may be a more appropriate remedy than criminal sanctions. In other situations, it may be necessary to institute disqualification proceedings in conjunction with criminal proceedings to assure that human subjects will be adequately protected.

138. FDA is adopting the conforming amendments as proposed. However, in accordance with the principles of common sense, the amendments proposed separately but applicable both to Part 50 and Part 56 have been combined and are included with FDA's informed consent final rule published elsewhere in this issue of the Federal Register.

139. On its own initiative, the agency is also adopting amendments to the IDE regulations (21 CFR Part 812) to conform them to Part 56. The IDE regulations were promulgated by FDA after the August 14, 1979 reproposal of these regulations.

However, the agency has decided not to amend the IDE regulations for intraocular lenses (21 CFR Part 813). The ongoing intraocular lens investigations are exempt from the requirements established by these regulations under § 56.104(a). Therefore, it would not be appropriate to modify Part 813 at this time. In addition, the agency is revising Forms FD–1571, 1572, and 1573 in 21 CFR

312.1(a) to conform them to these regulations. FDA stated in the 1978 proposal (43 FR 35198) that it would revise these forms at the time the final IRB regulations were adopted.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701(a), 706, and 801, 52 Stat. 1049–1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–518 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–546, 560, 562–574 (21 U.S.C. 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371(a), 376, and 381)) and the Public Health Service Act (secs. 215, 351, 354–360F, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.1), Chapter I of Title 21 of the Code of Federal Regulations is amended as follows:

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. In Part 16, § 16.1 is amended by adding a new regulatory provision under paragraph (b)(2) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) * * *

Section 56.121(a), Relating to disqualifying an institutional review board or an institution.

2. By adding new Part 56, to read as follows:

PART 56—INSTITUTIONAL REVIEW BOARDS

Subpart A—General

Sec.

Subpart B—Organization and Personnel

Subpart C—IRB Functions and Operations

Subpart D—Records and Reports

Subpart E—Administrative Action for Noncompliance

Authority: Secs. 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701(a), 706, and 801, Pub. L. 717, 52 Stat. 1049–1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–518 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–546, 560, 562–574 (21 U.S.C. 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371(a), 376, and 381), secs. 215, 301, 351, 354–360f, Pub. L. 410, 58 Stat. 690, 702 as amended, 82 Stat. 1173–1186 as amended (42 U.S.C. 216, 241, 262, 263b–263n).

Subpart A—General Provisions

§ 56.101 Scope.

(a) This part contains the general standards for the composition, operation, and responsibility of an Institutional Review Board (IRB) that reviews clinical investigations regulated by the Food and Drug Administration under sections 505(i), 507(d), and 520(g) of the act, as well as clinical investigations that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products. Compliance with this part is intended to protect the rights and welfare of human subjects involved in such investigations.

(b) References in this part to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21, unless otherwise noted.

§ 56.102 Definitions.

As used in this part:

(a) "Act" means the Federal Food, Drug, and Cosmetic Act, as amended (secs. 201–902, 52 Stat. 1040 et seq., as amended (21 U.S.C. 321–392)).

(b) "Application for research or marketing permit" includes:

(1) A color additive petition, described in Part 71.

(2) Data and information regarding a substance submitted as part of the procedures for establishing that a substance is generally recognized as safe for a use which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food, described in § 170.35.

(3) A food additive petition, described in Part 171.

(4) Data and information regarding a food additive submitted as part of the procedures regarding food additives permitted to be used on an interim basis pending additional study, described in § 180.1.

(5) Data and information regarding a substance submitted as part of the procedures for establishing a tolerance for unavoidable contaminants in food and food-packaging materials, described in section 406 of the act.

(6) A "Notice of Claimed Investigational Exemption for a New Drug" described in Part 312.

(7) A new drug application, described in Part 314.

(8) Data and information regarding the bioavailability or bioequivalence of drugs for human use submitted as part of the procedures for issuing, amending, or repealing a bioequivalence requirement, described in Part 320.

(9) Data and information regarding an over-the-counter drug for human use submitted as part of the procedures for classifying such drugs as generally recognized as safe and effective and not misbranded, described in Part 330.

(10) Data and information regarding an antibiotic drug submitted as part of the procedures for issuing, amending, or repealing regulations for such drugs, described in Part 430.

(11) An application for a biological product license, described in Part 601.

(12) Data and information regarding a biological product submitted as part of the procedures for determining that licensed biological products are safe and effective and not misbranded, as described in Part 601.

(13) An "Application for an Investigational Device Exemption," described in Parts 812 and 813.

(14) Data and information regarding a medical device for human use submitted as part of the procedures for classifying such devices, described in Part 860.

(15) Data and information regarding a medical device for human use submitted as part of the procedures for establishing, amending, or repealing a standard for such device, described in Part 861.

(16) An application for premarket approval of a medical device for human use, described in section 515 of the act.

(17) A product development protocol for a medical device for human use, described in section 515 of the act.

(18) Data and information regarding an electronic product submitted as part of the procedures for establishing, amending, or repealing a standard for such products, described in section 358 of the Public Health Service Act.

(19) Data and information regarding an electronic product submitted as part of the procedures for obtaining a variance from any electronic product performance standard, as described in § 1010.4.

(20) Data and information regarding an electronic product submitted as part of the procedures for granting, amending, or extending an exemption from a radiation safety performance standard, as described in § 1010.5.

(21) Data and information regarding an electronic product submitted as part of the procedures for obtaining an exemption from notification of a radiation safety defect or failure of compliance with a radiation safety performance standard, described in Subpart D of Part 1003.

(c) "Clinical investigation" means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i), 507(d), or 520(g) of the act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of Part 58, regarding nonclinical laboratory studies. The terms "research," "clinical research," "clinical study," "study," and "clinical investigation" are deemed to be synonymous for purposes of this part.

(d) "Emergency use" means the use of a test article on a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval.

(e) "Human subject" means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient.

(f) "Institution" means any public or private entity or agency (including Federal, State, and other agencies). The term "facility" as used in section 520(g) of the act is deemed to be synonymous with the term "institution" for purposes of this part.

(g) "Institutional Review Board (IRB)" means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. The term has the same meaning as the phrase "institutional review committee" as used in section 520(g) of the act.

(h) "Investigator" means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject) or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team.

(i) "Minimal risk" means that the risks of harm anticipated in the proposed research are not greater, considering probability and magnitude, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

(j) "Sponsor" means a person or other entity that initiates a clinical investigation, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A person other than an individual (e.g., a corporation or agency) that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators.

(k) "Sponsor-investigator" means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

(l) "Test article" means any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354–360F of the Public Health Service Act.

§ 56.103 Circumstances in which IRB review is required.

(a) Except as provided in §§ 56.104 and 56.105, any clinical investigation which must meet the requirements for prior submission (as required in Parts 312, 812, and 813) to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB meeting the requirements of this part. The determination that a clinical investigation of this part.

(b) Except as provided in §§ 56.104 and 56.105, the Food and Drug Administration may decide not to consider in support of an application for a research or marketing permit any data or information that has been derived from a clinical investigation that has not been approved by, and that was not subject to initial and continuing review by, an IRB meeting the requirements may not be considered in support of an application for a research or marketing permit does not, however, relieve the applicant for such a permit of any obligation under any other applicable regulations to submit the results of the investigation to the Food and Drug Administration.

(c) Compliance with these regulations will in no way render inapplicable pertinent Federal, State, or local laws or regulations.

§ 56.104 Exemptions from IRB requirement.

The following categories of clinical investigations are exempt from the requirements of this part for IRB review:

(a) Any investigation which commenced before July 27, 1981, and was subject to requirements for IRB review under FDA regulations before that date, provided that the investigation remains subject to review of an IRB which meets the FDA requirements in effect before July 27, 1981.

(b) Any investigation commenced before July 27, 1981, and was not otherwise subject to requirements for IRB review under Food and Drug Administration regulations before that date.

(c) Emergency use of a test article, provided that such emergency use is reported to the IRB within 5 working days. Any subsequent use of the test article at the institution is subject to IRB review.

§ 56.105 Waiver of IRB requirement.

On the application of a sponsor or sponsor-investigator, the Food and Drug Administration may waive any of the requirements contained in these

regulations, including the requirements for IRB review, for specific research activities or for classes of research activities, otherwise covered by these regulations.

Subpart B—Organization and Personnel

§ 56.107 IRB membership.

(a) Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution. The IRB shall be sufficiently qualified through the experience and expertise of its members, and the diversity of the members' backgrounds including consideration of the racial and cultural backgrounds of members and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review specific research activities, the IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. If an IRB regularly reviews research that involves a vulnerable category of subjects, including but not limited to subjects covered by other parts of this chapter, the IRB should include one or more individuals who are primarily concerned with the welfare of these subjects.

(b) No IRB may consist entirely of men, or entirely of women, or entirely of members of one profession.

(c) Each IRB shall include at least one member whose primary concerns are in nonscientific areas; for example: lawyers, ethicists, members of the clergy.

(d) Each IRB shall include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution.

(e) No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

(f) An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of complex issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

Subpart C—IRB Functions and Operations

§ 56.108 IRB functions and operations.

In order to fulfill the requirements of these regulations, each IRB shall:

(a) Follow written procedures (1) for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution, (2) for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review, (3) for insuring prompt reporting to the IRB of changes in a research activity, (4) for insuring that changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects; and (5) for insuring prompt reporting to the IRB of unanticipated problems involving risks to subjects or others.

(b) Except when an expedited review procedure is used (see § 56.110), review proposed research at convened meetings at which a majority of the members of the IRB are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it shall receive the approval of a majority of those members present at the meeting.

(c) Be responsible for reporting to the appropriate institutional officials and the Food and Drug Administration any serious or continuing noncompliance by investigators with the requirements and determinations of the IRB.

§ 56.109 IRB review of research.

(a) An IRB shall review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by these regulations.

(b) An IRB shall require that information given to subjects as part of informed consent is in accordance with § 50.25. The IRB may require that information, in addition to that specifically mentioned in § 50.25, be given to the subjects when in the IRB's judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

(c) An IRB shall require documentation of informed consent in accordance with § 50.27, except that the IRB may, for some or all subjects, waive the requirement that the subject or the subject's legally authorized representative sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context. In cases where the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding the research.

(d) An IRB shall notify investigators and the institution in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity. If the IRB decides to disapprove a research activity, it shall include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

(e) An IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.

§ 56.110 Expedited review procedures for certain kinds of research involving no more than minimal risk, and for minor changes in approved research.

(a) The Food and Drug Administration has established, and published in the **Federal Register**, a list of categories of research that may be reviewed by the IRB through an expedited review procedure. The list will be amended, as appropriate, through periodic republication in the **Federal Register**.

(b) An IRB may review some or all of the research appearing on the list through an expedited review procedure, if the research involves no more than minimal risk. The IRB may also use the expedited review procedure to review minor changes in previously approved research during the period for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure set forth in § 56.108(b).

(c) Each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

(d) The Food and Drug Administration may restrict, suspend, or terminate an institution's or IRB's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

§ 56.111 Criteria for IRB approval of research.

(a) In order to approve research covered by these regulations the IRB shall determine that all of the following requirements are satisfied:

(1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by Part 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by § 50.27.

(6) Where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(b) Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as persons with acute or severe physical or mental illness, or persons who are economically or educationally disadvantaged, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.

§ 56.112 Review by institution.

Research covered by these regulations that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

§ 56.113 Suspension or termination of IRB approval of research.

An IRB shall have authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the investigator, appropriate institutional officials, and the Food and Drug Administration.

§ 56.114 Cooperative research.

In complying with these regulations, institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.

Subpart D—Records and Reports

§ 56.115 IRB records.

(a) An institution, or where appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

(1) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(2) Minutes of IRB meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IRB; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the IRB and the investigators.

(5) A list of IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's chief anticipated contributions to IRB deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, stockholder, paid or unpaid consultant.

(6) Written procedures for the IRB as required by § 56.108(a).

(7) Statements of significant new findings provided to subjects, as required by § 50.25.

(b) The records required by this regulation shall be retained for at least 3 years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of the Food and Drug Administration at reasonable times and in a reasonable manner.

(c) The Food and Drug Administration may refuse to consider a clinical investigation in support of an application for a research or marketing permit if the institution or the IRB that reviewed the investigation refuses to allow an inspection under this section.

Subpart E—Administrative Actions for Noncompliance

§ 56.120 Lesser administrative actions.

(a) If apparent noncompliance with these regulations in the operation of an IRB is observed by an FDA investigator during an inspection, the inspector will present an oral or written summary of observations to an appropriate representative of the IRB. The Food and Drug Administration may subsequently send a letter describing the noncompliance to the IRB and to the parent institution. The agency will require that the IRB or the parent institution respond to this letter within a time period specified by FDA and describe the corrective actions that will be taken by the IRB, the institution, or both to achieve compliance with these regulations.

(b) On the basis of the IRB's or the institution's response, FDA may schedule a reinspection to confirm the adequacy of corrective actions. In addition, until the IRB or the parent institution takes appropriate corrective action, the agency may:

(1) Withhold approval of new studies subject to the requirements of this part that are conducted at the institution or reviewed by the IRB;

(2) Direct that no new subjects be added to ongoing studies subject to this part;

(3) Terminate ongoing studies subject to this part when doing so would not endanger the subjects; or

(4) When the apparent noncompliance creates a significant threat to the rights and welfare of human subjects, notify relevant State and Federal regulatory agencies and other parties with a direct

interest in the agency's action of the deficiencies in the operation of the IRB.

(c) The parent institution is presumed to be responsible for the operation of an IRB, and the Food and Drug Administration will ordinarily direct any administrative action under this subpart against the institution. However, depending on the evidence of responsibility for deficiencies, determined during the investigation, the Food and Drug Administration may restrict its administrative actions to the IRB or to a component of the parent institution determined to be responsible for formal designation of the IRB.

§ 56.121 Disqualification of an IRB or an institution.

(a) Whenever the IRB or the institution has failed to take adequate steps to correct the noncompliance stated in the letter sent by the agency under § 56.120(a), and the Commissioner of Food and Drugs determines that this noncompliance may justify the disqualification of the IRB or of the parent institution, the Commissioner will institute proceedings in accordance with the requirements for a regulatory hearing set forth in Part 16.

(b) The Commissioner may disqualify an IRB or the parent institution if the Commissioner determines that:

(1) The IRB has refused or repeatedly failed to comply with any of the regulations set forth in this part, and

(2) The noncompliance adversely affects the rights or welfare of the human subjects in a clinical investigation.

(c) If the Commissioner determines that disqualification is appropriate, the Commissioner will issue an order that explains the basis for the determination and that prescribes any actions to be taken with regard to ongoing clinical research conducted under the review of the IRB. The Food and Drug Administration will send notice of the disqualification to the IRB and the parent institution. Other parties with a direct interest, such as sponsors and clinical investigators, may also be sent a notice of the disqualification. In addition, the agency may elect to publish a notice of its action in the Federal Register.

(d) The Food and Drug Administration will not approve an application for a research permit for a clinical investigation that is to be under the review of a disqualified IRB or that is to be conducted at a disqualified institution, and it may refuse to consider in support of a marketing permit the data from a clinical investigation that was reviewed by a disqualified IRB as conducted at a disqualified institution, unless the IRB or the parent institution is reinstated as provided in § 56.123.

§ 56.122 Public disclosure of information regarding revocation.

A determination that the Food and Drug Administration has disqualified an institution and the administrative record regarding that determination are disclosable to the public under Part 20.

§ 56.123 Reinstatement of an IRB or an institution.

An IRB or an institution may be reinstated if the Commissioner determines, upon an evaluation of a written submission from the IRB or institution that explains the corrective action that the institution or IRB plans to take, that the IRB or institution has provided adequate assurance that it will operate in compliance with the standards set forth in this part. Notification of reinstatement shall be provided to all persons notified under § 56.121(c).

§ 56.124 Actions alternative or additional to disqualification.

Disqualification of an IRB or of an institution is independent of, and neither in lieu of nor a precondition to, other proceedings or actions authorized by the act. The Food and Drug Administration may, at any time, through the Department of Justice institute any appropriate judicial proceedings (civil or criminal) and any other appropriate regulatory action, in addition to or in lieu of, and before, at the time of, or after, disqualification. The agency may also refer pertinent matters to another Federal, State, or local government agency for any action that that agency determines to be appropriate.

Effective date. This regulation shall become effective July 27, 1981.

(Secs. 406, 408, 409, 501, 502, 503, 505, 506, 507, 510, 513–516, 518–520, 701(a), 706, and 801, 52 Stat. 1049–1054 as amended, 1055, 1058 as amended, 55 Stat. 851 as amended, 59 Stat. 463 as amended, 68 Stat. 511–517 as amended, 72 Stat. 1785–1788 as amended, 74 Stat. 399–407 as amended, 76 Stat. 794–795 as amended, 90 Stat. 540–560, 562–574 (21 U.S.C. 346, 346a, 348, 351, 352, 353, 355, 356, 357, 360, 360c–360f, 360h–360j, 371(a) 376, and 381); secs. 215, 301, 351, as amended (42 U.S.C. 216, 241, 262, 263b–263n))

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 81-2886 Filed 1-26-81; 8:45 am]

BILLING CODE 4110-03-M

21 CFR Part 50

[Docket No. 78N-0049]

Protection of Human Subjects; Prisoners Used as Subjects in Research; Correction

AGENCY: Foqd and Drug Administration.

ACTION: Correction.

SUMMARY: In FR Doc. 80–16578 appearing at page 36386 in the Federal Register of Friday, May 30, 1980, the following correction is made in the first column of page 36391: In § 50.1 *Scope*, in paragraph (a) the word "prisoner" is removed.

FOR FURTHER INFORMATION CONTACT: Agnes Black, Federal Register Writer (HFC–11), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–2994.

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 81-2889 Filed 1-21-81; 8:45 am]

BILLING CODE 4110-03-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 77N-0350]

Protection of Human Research Subjects; Clinical Investigations Which May Be Reviewed Through Expedited Review Procedure Set forth in FDA Regulations

AGENCY: Food and Frug Administration.

ACTION: Notice.

SUMMARY: This notice contains a list of research activities which institutional review boards may review through the expedited review procedures set forth in FDA regulations for the protection of human research subjects.

FOR FURTHER INFORMATION CONTACT: John C. Petricciani, Office of the Commissioner (HFB–4), Food and Drug Administration, 8800 Rockville Pike, Bethesda, MD 20205, 301–496–9320.

SUPPLEMENTARY INFORMATION: Elsewhere in this issue of the **Federal Register**, the Food and Drug Administration (FDA) is publishing final regulations establishing standards for institutional review boards (IRBs) for clinical investigations relating to the protection of human subjects in research. Section 56.110 (21 CFR 56.110) of the final IRB regulations provides that the agency will publish in the **Federal Register** a list of categories of research activities, involving no more than minimal risk, that may be reviewed by an IRB through expedited review procedures. This notice is published in accordance with § 56.110.

The agency concludes that research activities with human subjects involving no more than minimal risk and involving one or more of the following categories (carried out through standard methods), may be reviewed by an IRB through the expedited review procedure authorized in § 56.110.

(1) Collection of hair and nail clippings in a non-disfiguring manner; of deciduous teeth; and of permanent teeth if patient care indicates a need for extraction.

(2) Collection of excreta and external secretions including sweat and uncannulated saliva; of placenta at delivery; and of amniotic fluid at the time of rupture of the membrane before or during labor.

(3) Recording of data from subjects who are 18 years of age of older using noninvasive procedures routinely employed in clinical practice. This category includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy. It also includes such procedures as weighting, electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, diagnostic echography, and electroretinography. This category does not include exposure to electromagnetic radiation outside the visible range (for example, x-rays or microwaves).

(4) Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an eight-week period and no more often than two times per week, from subjects who are 18 years of age or older and who are in good health and not pregnant.

(5) Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of the teeth, and the process is accomplished in accordance with accepted prophylactic techniques.

(6) Voice recordings made for research purposes such as investigations of speech defects.

(7) Moderate exercise by healthy volunteers.

(8) The study of existing data, documents, records, pathological specimens, or diagnostic specimens.

(9) Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

This list will be amended as appropriate and a current list will be published periodically to the **Federal Register.**

Dated: January 19, 1981.

Jere E. Goyan,

Commissioner of Food and Drugs.

[FR Doc. 81-2690 Filed 1-21-81; 3:59 pm]

BILLING CODE 4110-03-M

federal register

Tuesday
January 27, 1981

Part X

Environmental Protection Agency

Tampering Enforcement Regulations

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 85

[EN FRL 1718-4]

Tampering Enforcement Regulations

AGENCY: Environmental Protection Agency.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Environmental Protection Agency (Agency or EPA) is considering amending Part 85 of Title 40 of the Code of Federal Regulations by adding a subpart establishing tampering enforcement regulations.

The Agency receives frequent inquiries, particularly from various segments of the automotive industry, about the prohibitions against "tampering" that appear in Section 203 (a)(3) of the Clean Air Act. The purpose of this rulemaking is to clarify EPA's tampering enforcement policy for vehicle manufacturers, dealers, fleet operators, independent repair shops, consumers, and others.

DATES: EPA will consider comments received on or before March 30, 1981, in developing a Notice of Proposed Rulemaking or Interim Final Regulations or policy statement, as appropriate.

ADDRESSES: *Comments.* Send written comments to: Central Docket Section (A-130), U.S. Environmental Protection Agency, Attn: Docket No. EN-80-2, 401 M Street, S.W., Washington, D.C. 20460.

Docket. Copies of materials relevant to this rulemaking proceeding are contained in Public Docket EN-80-2 at the Central Docket Section of the U.S. Environmental Protection Agency, West Tower Lobby, Gallery 1, 401 M Street, S.W., Washington, D.C. The docket is available for review between the hours of 8:00 a.m. and 4:00 p.m. Monday through Friday. As provided in 40 CFR Part 2, a reasonable fee may be charged for copying services.

FOR FURTHER INFORMATION CONTACT: Mrs. Barbara Giliberti, Field Operations and Support Division (EN-397), U.S. Environmental Protection Agency, 401 M Street, S.W., Washington, D.C. 20460, (202) 472-9350.

SUPPLEMENTARY INFORMATION:

I. Background

Section 203(a)(3) of the Clean Air Act (Act), 42 U.S.C. § 7522(a)(3), prohibits "tampering" with the emission control systems of motor vehicles. The Section reads as follows:

Sec. 203. (a) The following acts and the causing thereof are prohibited—

(3)(A) for any person to remove or render inoperative any device or element of design installed on or in a motor vehicle or motor vehicle engine in compliance with regulations under this title prior to its sale and delivery to the ultimate purchaser, or for any manufacturer or dealer knowingly to remove or render inoperative any such device or element of design after such sale and delivery to the ultimate purchaser; or

(B) for any person engaged in the business of repairing, servicing, selling, leasing or trading motor vehicles or motor vehicle engines, or who operates a fleet of motor vehicles, knowingly to remove or render inoperative any device or element of design installed on or in a motor vehicle or motor vehicle engine in compliance with regulations under this title following its sale and delivery to the ultimate purchaser.

Section 205 of the Act provides for a maximum civil penalty of $10,000 for any manufacturer, dealer or other person who violates paragraph (3)(A) of Section 203(a) and of $2,500 for any person who violates paragraph (3)(B) of Section 203(a). Section 205 further provides that any such violation shall constitute a separate offense with respect to each motor vehicle or motor vehicle engine. Section 204 of the Act provides for injunctive relief against violations of Section 203(a).

EPA's primary objective in enforcing the tampering prohibition is to assure the unimpaired operation of motor vehicle emission controls. According to EPA emission estimates, motor vehicles account for nearly three-quarters of the total carbon monoxide, over one-third of the hydrocarbons, and one-third of the oxides of nitrogen emitted to the atmosphere.[1] In urban areas, these percentages may be higher. These emissions contribute to a wide variety of medical problems, including anemia, heart strain, headaches, and lung and eye irritation. The unimpaired operation of emission controls is necessary to ensure reductions in these harmful emissions.

A survey conducted by EPA in 1979 [2] indicated that approximately 18 percent of the 1973-1980 model year motor vehicle fleet had been subjected to obvious tampering, e.g., tampering with the EGR system. An additional 46.5% showed at least one item in the arguably tampered (potential, but not clear-cut tampering) category, e.g., the idle limiter cap was missing.[3] The increased emissions from this portion of the fleet have a substantial adverse impact on air quality and, in turn, on human health.

At present, the main sources of guidance as to the Agency's enforcement policy are statements contained in letters responding to particular concerns and in Mobile Source Enforcement Memorandum 1A (Memo 1A).[4] This memorandum, entitled Interim Tampering Enforcement Policy, was issued on June 25, 1974, prior to the 1977 amendments to the Act. Those amendments extended the prohibition on post-sale tampering to include any person engaged in the business of repairing, servicing, selling leasing or trading motor vehicles or motor vehicle engines or who operates a fleet of motor vehicles.

The specific language of Memo 1A addresses only dealers and vehicle and engine manufacturers. This is because, at the time Memo 1A was prepared, the post-sale tampering prohibition applied only to dealers and manufacturers. In August of 1977, Section 203(a)(3)(B) was added to the Act, and that prohibition was extended to include the parties listed above. The policy enunciated in Memo 1A has been interpreted as extending to these parties, and some of them have expressed concern with EPA's interpretation of the prohibition.

A substantial amount of concern exists in the industry as to what constitutes a violation of the tampering prohibition. EPA has received numerous inquiries requesting further interpretation of the statute. In some cases, the confusion over the meaning of the tampering prohibition may have led to people refraining from acceptable activities because of fear of being held liable for tampering.

The Agency is considering the development of rules describing specific acts which, in its view, constitute tampering in order to provide more guidance to those parties affected and to encourage uniform compliance. The regulations would be intended:

(1) To inform the public of EPA's present enforcement policies; and

(2) To respond to other concerns of the public, such as what types of vehicle "modifications" or "repairs" are tampering and to interpret further the "causing" language of the statute.

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[1] National Enforcement Investigations Center and Field Operations and Support Division, U.S. Environemtnal Protection Agency, "Motor Vehicle Tampering Survey—1979" (May 1980).

[2] *Id.*, at 3.

[3] Carburetors are set to the proper fuel-air mixture at the factory. Limiter caps are then placed on the idle mixture screws to prevent misadjustments. Misadjustments will usually cause a significant increase in CO emissions. Enrichments producing greater than about 1% CO in the exhaust do not provide enough oxygen for the correct oxidizing function of the catalyst. As a result, the vehicle usually exceeds EPA standards. Because idle limiter cap removal was so prevalent that to place it in the tampered category would obscure the rest of the data, vehicles on which limiter caps were missing or disconnected were placed in the "arguably tampered" category.

[4] A copy of Memo 1A is in Public Docket EN-80-2.

II. Discussion

Section 203(a)(3) of the Act does not require that a vehicle exceed emission standards in order for a tampering violation to occur; it simply prohibits the act of removing or rendering inoperative any emission control device or element of design. Therefore, a tampering violation may have been committed if a motor vehicle emission control system is changed from its original certified configuration by a person subject to the Section 203(a)(3) tempering prohibition. It has been suggested that EPA adopt a policy of enforcement only if the act in question causes an increase in vehicle emissions or causes emissions to exceed standards. Such a policy may require performing the expensive and time-consuming Federal Test Procedure on each vehicle for which tampering is alleged.

Although the Agency has interpreted § 203(a)(3) in Memo 1A (and has interpreted Memo 1A on a case-by-case basis in response to inquiries), some members of the industry have expressed concern about the scope of the provision and EPA's enforcement policy. Following is a partial list of the areas about which the public has inquired:

(1) The potential liability of a repair facility which works on a vehicle that has been subjected to previous tampering;

(2) The potential liability, under the "causing" language, of part suppliers who sell, but do not install, parts the installation of which may involve the removal or rendering inoperative of an emission control device. An example of such a part is a straight pipe which could replace a catalytic converter;

(3) The acts which might be viewed as completing an act of tampering and the potential liability associated with such acts;

(4) The potential liability, under the "causing" language, of publishers or distributors of emission control "bypass" manuals;

(5) The potential liability of people who convert vehicles to alternative fuels or exhaust systems;

(6) The potential liability of manufacturers of aftermarket turbochargers and catalytic converters, and other add-on and replacement parts;

(7) The policy of the Agency towards add-on accessories which could cause a vehicle to fail to meet standards but which do not involve physical removal or adjustment of an emission-related component;

(8) The applicability of the tampering prohibition to "racing vehicles";

(9) The policy of the Agency towards replacement of parts on which an act of tampering has already been completed;

(10) The definition of a fleet operator;

(11) The potential liability of a person who converts a California-version car to a 49-State version, and vice versa; and

(12) The potential liability of a person who "engine switches."

This is not an exclusive list of the areas which may be considered. The Agency would like comments on all aspects of tampering. EPA is particularly interested in learning what questions the public has about the tampering prohibition and about EPA's tampering policy as expressed in Memo 1A, and in suggestions about how these concerns may be reasonably resolved. EPA's responses to these questions, as well as to others which may arise, will be provided during the rulemaking process.

The Federal prohibition against tampering does not require the promulgation of regulations in order to become effective; Section 203(a)(3) can be and is being enforced as it stands. The Agency notes that a considerable period of time is involved in a full rulemaking. For these reasons, and because many people in the automotive industry have indicated a need to know how EPA's tampering enforement policy specifically applies to them, EPA is interested in receiving comments from affected parties as to whether the Agency should issue interim final regulations rather than proposed rules. The interim final rules would take effect upon publication, and the public would have 60 days to comment on them. The rules would them be modified, as appropriate, and republished. Another possibility is for the Agency to prepare a general statement concerning its tampering enforcement policy in lieu of rulemaking.

Proposed regulations, interim final regulations or a general policy statement, as appears appropriate, will be issued as soon as practicable after the end of the comment period provided by this notice.

This advance notice of proposed rulemaking is issued under the authority of Sections 203 and 301 of the Clean Air Act, 42 U.S.C. §§ 7522 and 7601.

Dated: January 19, 1981.

Douglas M. Costle,

Administrator.

[FR Doc. 81-2915 Filed 1-26-81; 8:45 a.m.]

BILLING CODE 6560-33-M

federal register

Tuesday
January 27, 1981

Part XI

Environmental Protection Agency

Agency Policy to Premanufacture Testing of New Chemical Substances and Announcement of Rescheduled Meeting and Extension of Comment on Certain Environmental Test Standards

ENVIRONMENTAL PROTECTION AGENCY

40 CFR Part 720

[OPTS 50024; TSH-FRL 1720-1]

New Chemical Substances; Premanufacture Testing Policy

AGENCY: Environmental Protection Agency (EPA).

ACTION: Proposed rule related notice.

SUMMARY: This document announces existing Agency policy concerning an approach to premanufacture testing of new chemical substances. It identifies types of test data concerning physical and chemical properties and health and environmental effects which the Agency recommends be developed by manufacturers planning to manufacture a new chemical substance. This document also identifies test protocols which the Agency recommends be utilized to develop these data. The data elements identified here are those under consideration by the Organization for Economic Cooperation and Development (OECD) as recommended "Minimum Pre-market Data" (MPD) for premarket assessment in the OECD member nations.

FOR FURTHER INFORMATION CONTACT: John B. Ritch, Director, Industry Assistance Office (TS-799), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Rm E-229, 401 M St. SW, Washington, D.C. 20460, Toll free: (800-424-9065). In Washington, D.C.: (202-544-1404).

SUPPLEMENTARY INFORMATION:

I. Introduction

The Toxic Substances Control Act (TSCA), 15 U.S.C. 2601 *et seq.*, establishes a national policy that "adequate data should be developed with respect to the effect of chemical substances and mixtures on health and the environment and that the development of such data should be the responsibility of those who manufacture and those who process such chemical substances and mixtures" (sec. 2(b)(1)). TSCA section 5 establishes a premanufacture notification program and requires the submission of health and environmental effects test data which are in the possession or control of the intended manufacturer or processor of new chemical substances. However, TSCA does not establish a requirement that premanufacture testing be performed on all new chemical substances.

To encourage the voluntary development of premanufacture health and environmental effects test data, EPA has devoted extensive attention to development of a premanufacture testing policy in both national and international forums. EPA reached concensus on such testing within the framework of the Organization for Economic Cooperation and Development (OECD), an international organization of twenty-four nations that includes the major chemical producing nations of the non-communist world. The Agency has considered numerous approaches to premanufacture testing and has solicited and reviewed public comments on both policy and technical aspects of such testing. This document describes the Agency's premanufacture testing policy. It describes a base set of data that the Agency recommends as a starting point for premanufacture testing; and it calls for flexibility and the exercise of professional judgment in utilization of the base set. A number of test protocols are recommended for use in developing the base set data.

II. Background

Under section 5 of the Toxic Substances Control Act (TSCA), 15 U.S.C. section 2604, any person who intends to manufacture or import a new chemical substance for commercial purposes in the United States must submit notice to the Environmental Protection Agency (EPA) at least ninety days before he commences manufacture or import.

Section 3(9) defines a "new chemical substance" as any chemical substance which is not included on the list, or "inventory," of existing chemical substances compiled by EPA under section 8(b). Notices of availability of the Inventory were published in the **Federal Register** of May 15, 1979 (44 FR 28558) and revised on July 29, 1980 (45 FR 50544). As required by section 5, the requirement for premanufacture notification became effective thirty days later on July 1, 1979.

Section 5(d)(1) of the Act defines the contents of a premanufacture notice. It requires the manufacturer to report certain information described in section 8(a)(2), e.g., chemical identity, uses, and exposure data. In addition, section 5(d)(1) requires the submission of test data, in the possession or control of the person submitting the notice, which are related to the effects on health or the environment from the manufacture, processing, distribution in commerce, use, and disposal of the chemical substance. Section 5 does not require that particular tests be performed on all new chemical substances before submission of premanufacture notices.

EPA proposed premanufacture notification requirements and review procedures published in the **Federal Register** of January 10, 1979 (44 FR 2242), together with a reporting form for submission of the information required by Section 5(d)(1). After consideration of the public comments on this proposal, EPA reproposed the reporting form and certain of the reporting requirements published in the **Federal Register** of October 16, 1979 (44 FR 59764). The proposed form and reporting requirements provide a format for submission of data from health and environmental testing. However, they do not require that particular tests be performed.

EPA issued and requested comments on a discussion of premanufacture testing policy and technical issues published in the **Federal Register** of March 16, 1979 (44 FR 16240). The discussion document noted that EPA was considering publishing voluntary premanufacture testing guidance and presented several approaches to constructing such guidance, including the use of a base set.

Seventy-one public comments were received, most of them from chemical manufacturers and trade associations. Most industry commentors recommended that EPA not publish guidance, while a few commentors expressed the view that testing guidance would be of significant benefit to the premanufacture notice program.

The most common argument against publishing premanufacture testing guidance was that the statute does not expressly authorize EPA to publish such testing guidance and, should EPA publish voluntary testing guidance, the Agency would effectively make its use mandatory by using the guidance as a "checklist" for evaluating data adequacy of premanufacture notices.

The Agency believes that it has the authority to publish a non-binding policy statement under section 5. Moreover, the Agency is convinced that the publication of a non-binding policy statement on premanufacture testing is in the public interest. EPA has received numerous individual informal requests from manufacturers to provide guidance for new chemical testing. This policy statement reflects the present Agency policy concerning appropriate new chemical testing and makes it available to the general public. Until such time as this policy is modifed, the Agency will use the base set of data described herein as the starting point for constructing recommended premanufacture testing programs for purposes of both informal requests for guidance and petitions for such guidance submitted under section 4(g) of TSCA.

In response to the second concern mentioned above, the Agency recognizes that it cannot use testing guidance published under section 5 to establish a *de facto* general testing requirement for new chemicals. Section 5(b)(1)(A) provides the mechanism for establishing testing requirements for certain new chemicals. Under section 5(b)(1)(A), a manufacturer of a new chemical subject to a section 4 test rule must submit the test data specified in the rule as part of the premanufacture notice required by section 5.

EPA is exploring ways to apply section 4 test rules to categories of chemical substances as authorized by section 26(c). Once category test rules are in effect, a new chemical substance which is a member of the defined category will be subject to the testing requirements as provided by section 5(b)(1)(A).

Another frequent comment was that, if EPA does recommend a base set, there should be flexibility in its application; i.e., that the manufacturer should retain discretion to modify it to suit various situations that may arise. These commentators stated that a "rigid" base set would preclude scientific discretion to tailor chemical testing to particular chemicals and production and use patterns. The Agency agrees with this comment. The policy calls for use of the base set as a starting point for testing but recognizes that particular circumstances of chemical characteristics and production/use patterns may justify deletion, substitution, or addition of data components. Either more or less testing than reflected by the base set of data may result. The Agency requests that companies which utilize the recommended base set to formulate their testing program for a new chemical explain deletions from or substitutions in the recommended base set.

The premanufacture testing policy contains two basic elements: (1) a base set of data which EPA recommends be developed by manufacturers and (2) recommended test protocols for developing the data. Both elements incorporate the results of international testing harmonization efforts of the Organization for Economic Cooperation and Development (OECD). EPA has been an active participant in this work for the past three years. Harmonization of chemical testing among nations is necessary to improve national controls, to efficiently utilize scarce resources, and to avoid unnecessary barriers to international trade. For these reasons, the development of consistent data requirements and testing methods was identified as a priority issue at the international level by the OECD in 1977.

The efforts to reach agreement on chemical testing have proceeded under tha aegis of the Chemicals Group of the OECD. Five expert groups, each under the leadership of individual member countries, were mandated to prepare, by the end of 1979, "state of the art" reports on mutally agreed, scientifically sound test methods for developing data for the prediction of chemical risk. These groups and lead countries were:

Group and Country

Physical/Chemical Properties—Federal Republic of Germany
Ecotoxicology—Netherlands
Degredation-accumulation A Japan, Federal Republic of Germany
Long-term Toxicology—United States
Short-term Toxicology—United Kingdom

A sixth expert group under the leadership of Sweden, called the Step Systems Group, considered the concept of step-sequence (tiered) testing systems. Based in part on the work of the other expert groups, the Step Systems Group was mandated to develop a step sequence testing scheme, including a recommended minimum premarket data set, for use by member countries in the assessment of new chemical substances.

Approximately 350 government and industry experts from all over the world have participated directly in the work of these expert groups. U.S. participants from government and industry numbered about twenty-five. In addition, the work of these groups has been formally reviewed and commented upon by the major international business and trade union organizations, the OECD Business and Industry Advisory Committee (BIAC), the OECD Trade Union Advisory Committee (TUAC), and a number of U.S. chemical manufacturers, trade associations, and environmental organizations.

With minor exceptions, the final reports of the five expert groups on testing were completed by the end of 1979 and all are complete at this time. These groups developed approximately 44 separate test methods (called "test guidelines" in OECD documents). Some of these test methods are considered final, while others are still undergoing inter-laboratory validation. In addition, most of the final reports from these groups identified particular tests which are appropriate for providing data for a premarket assessment.

Based in part on the work of these groups, the Expert Group on Step Systems produced a preliminary final report which contained a recommended premarket base set of data called the "Minimum Premarket Data" set (MPD).

The reports of all six expert groups were made available for public comment in the U.S. in April, 1980. (See "Organization for Economic Cooperation and Development (OECD) Chemicals Program; Final Reports on Testing Guidelines; Notice of Availability, "published in the **Federal Register** of April 17, 1980 (45 FR 26129).) Thrity-one comments were received. Commentators were divided on the Step Systems Group report, which recommended flexible application of the MPD. Three commentators supported the MPD, and one recommended against its use by EPA. Several other commentators expressed reservation about the use of the MPD and stressed the need for flexibility in its application.

Most commentators felt that the expert group reports containing test protocols were of high quality. Several commentators stressed the need for some flexibility in the recommended OECD test procedures, and there were numerous technical comments on the procedures themselves. These comments were considered by EPA and the U.S. delegation to the High Level Meeting of the OECD Chemicals Group, which took place in May, 1980.

Environmental ministers and senior officials from other concerned regulatory agencies of the OECD member nations met in May, 1980, to review the work of the expert groups and to make recommendations to the OECD Council concerning disposition of various work products. At that meeting, the participants endorsed the work of the expert groups and recommended that the final test methods be adopted and that draft methods be made final. In addition, they endorsed the minimum premarket set of data developed by the Step Systems Group and recommended that it and the various test guidelines be provisionally applied in member countries pending approval by the OECD Council. In December, 1980, the Environment Committee of the OECD also endorsed the MPD and test guidelines and recommended that the OECD Council publish both as a Council decision, which would make them binding on member nations. EPA anticipates that the OECD Council will issue a decision on the MPD and test guidelines early next year.

The base set of data which EPA is recommending herein is identical to the MPD developed by the OECD. The term "base set" will be used in this notice to denote the MPD.

It is recognized within the OECD working groups that, although the recommended base set tests are

generally applicable to new chemicals, not all may be applicable in certain circumstances. The OECD working groups also recognize that additional testing beyond the base set may be appropriate for some chemicals, as indicated by base set test results and/or circumstances of use and exposure. Current OECD plans are to develop general "flexibility criteria" to provide guidance concerning deviations from the recommended set of tests. EPA plans to incorporate such flexibility criteria into its premanufacture testing policy as the criteria are developed by the OECD.

The base set is the first step in the step sequence testing scheme that is being developed by the OECD. EPA will continue to participate in efforts to develop the remainder of the step sequence scheme. As further steps are agreed upon in the OECD, EPA plans to modify the premanufacture testing policy stated here accordingly.

In addition to these international testing harmonization efforts, EPA as been active in efforts of the Interagency Regulatory Liaison Group (RLG) to harmonize testing methodologies among the U.S. chemical regulatory agencies. The IRLG is comprised of representatives from the Consumer Product Safety Commission, the Food and Drug Administration, the Occupational Safety and Health Administration, and the Department of Agricultural Food Safety and Quality Service in addition to EPA. The National Toxicology Program (represented by the National Cancer Institute), the Department of Commerce, and the Department of Energy have participated as advisors.

The purpose of the IRLG effort is to develop uniform testing methodologies to provide data for chemical assessment purposes. To date, the IRLG has, after public review, finalized test standards for acute oral toxicity, acute dermal toxicity, acute eye irritation, and teratology. Test standards for a number of other health effects, as well as for envionmental effects and physical chemical properties, are under development. These standards, which will be consistent with the OECD test guidelines, will be published for public comment by the IRLG during the coming months.

III. Policy Statment

EPA recommends that manufacturers of a new chemical substance subject to the premanufacture notification requirements of TSCA utlize the base set of data listed below as a starting point for designing a premanufacture testing program.

A. Recommended Base Set

1. Physical/Chemical Data:

Melting point/melting range
Boiling point/boiling range
Density of liquids and solids
Vapor pressure
Water solubility
Partition coefficient, n-octanol/water
Hydrolysis (as a function of pH)
Spectra (UV and visible)
Soil adsorption/desorption
Dissociation constant
Particle size distribution

2. Acute Toxicity Data:

Actute oral toxicity
Actute dermal toxicity
Actute inhalation toxicity
Skin irritation
Skin sensitization
Eye irritation (for chemicals showing no skin irritation)

3. Repeated Dose Toxicity Data:

14–28 days, repeated dose test(s) using probable routes(s) of human exposure

4. Mutagenicity Data (Screening Tests):

Gene (point) mutation
Chromosome aberrations

5. Ecotoxicity Data:

Acute toxicity, LC_{50} study, fish (96 hour)
Daphnia reproduction study (3 broods)
Growth inhibition study, unicellular alga (4 days)

6. Degradation/Accumulation Data:

Ready Degradability
Bioaccumulation (uptake from medium)

B. Recommended Test Methodologies

EPA recommends that tests to provide the data elements listed above be performed according to methods published by the OECD, the IRLG, or by EPA test standards promulgated under section 4 of TSCA, section 3 of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or other approved EPA methods. In the absence of final test methods from one of these sources, other test methods which are generally accepted among professionals in the particular scientific field would be appropriate.

Sources for TSCA, FIFRA, and IRLG tests will be cited later in this notice. The OECD test guidelines will be published by OECD in early 1981. In addition, EPA plans to make them available from the Industry Assistance Office in the near future. They may be requested by calling the toll free number given earlier in this notice.

C. Modifications

The base set may be modified to suit particular chemicals and production/use patterns. For example, technical considerations may make some tests inapplicable for certain chemicals. Also, in some cases, the results of some physical/chemical properties tests may indicate that certain other tests are unnecessary or inappropriate. In circumstances of very low human exposure or environmental release, a lesser amount of testing may be warranted.

Other considerations may suggest that additional testing should be performed. For example, structure/activity analysis may suggest the need for testing for carcinogenic effects, which are not directly addressed in the base set. Similarly, circumstances of high potential human exposure or environmental release would generally indicate a need for additional testing. For example, in circumstances of repeated human exposure, a 90-day subchronic test and tests for teratogenic and reproductive effects would be recommended.

The screening-level base set data also may indicate the need for follow-up testing. For example, the data may indicate the need for oncogenicity, chronic toxicity, or additional ecological effects tests. EPA is continuing to study the relationship of various "follow-up" tests to the tests in the base set recommended here. In the future, the Agency expects to publish guidance concerning such relationships.

Similarly, particular circumstances may require modification of a test method. In such case, the modification should not reduce the effectivenss or accurracy of the test.

EPA requests persons using the recommended base set data as a starting point for premanufacture testing to explain the scientific rationale for any deletions, substitutions or additions to the base set. EPA also requests persons who modify a recommended test method, or who substitute a different test method, to provide the protocol and a scientific rationale for the change.

IV. Discussion

The recommended base set of data elements is intended to provide information which, in conjunction with required premanufacure information related to use and exposure, will permit an initial assessment of potential risk which a chemical substance may present to health or the environment. The base set of data was constructed with both scientific and economic considerations in mind. Each data element supplies information that is useful for risk assessment, as explained more fully below. Also data elements related to certain important effects, for

example teratogenicity and neurotoxicity, are not included in the base set because relatively inexpensive and reliable (validated) screening tests are not available.

A. Relationships To Section 5(e) Actions

Section 5(e) of TSCA authorizes EPA to prohibit or limit manufacture of a new chemical substance if the Agency does not have sufficient information to conduct a reasoned risk assessment but finds that the chemical may present an unreasonable risk or that it is or will be produced in substantial quantities and either enters or may reasonably be anticipated to enter the environment in substantial quantities or there is or may be significant or substantial human exposure to the substance. EPA will consider all available relevant information in determining whether to initiate a 5(e) action concerning a premanufacture notice. EPA will not automatically initiate 5(e) actions if a manufacturer declines to utilize the recommended base set or deviates from the base set.

B. Test Cost analysis

Since there are no published cost data for OECD test guidelines, EPA requested a contractor (Contract No. 68-01-5864) to develop an appropriate methodology and estimate the cost of these protocols. The methodology and analysis are presented in a separate document entitled *Cost Analysis Methodology and Protocol Estimates: OECD Minimum Premarket Data (MPD) Test Protocols*, January, 1981, which may be obtained from the information contact above. Because so me OECD test guidelines are not currently being used in the United States, the estimated costs shown below should be considered only representative of actual costs. The test costs are not additive since the total cost to a firm will be determined by the testing program devised and followed by that firm for each individual chemical. Because this policy statement establishes voluntary testing guidance rather than regulations, an economic impact analysis is not warranted.

The Agency has initiated a study of the over-all economic impacts of TSCA on the chemical industry. This study will examine changes in research and development programs for new chemicals including changes in testing as well as such effects as impacts on growth, innovation, and international trade. By looking at the impacts of all TSCA regulations (testing, premanufacturing notification, control actions, and reporting requirements), the Agency believes that it will be better able to analyze the economic impact of TSCA.

C. Base Set Data Elelments

The following discussion provides, for each base set data element, an explanation of its utility in performing a risk assessment, references to or sources for the recommended test protocols for each element, and available information on the estimated cost of performing the test according to the protocol.

1. *Physical/chemical properties.* (a) Melting Point/melting range. (1) Contribution to risk assessment. The melting point of a chemical is the temperature at which the solid and liquid forms of the chemical are in equilibrium. Data on melting point/melting range are useful for chemical fate and exposure analysis because they indicate the physical state of a chemical substance at ambient temperatures. This gives an indication of the distribution of the substance in the water, soil, and air. In addition, the melting point is important for identification purposes and, as a measure of purity, can give indication of impurities which may have environmental relevance. Melting point data may also be useful for the design of other tests of the chemical.

(2) Test protocols and estimated cost.
OECD: Estimated cost of test—$100.
IRLG: None.
TSCA, section 4: Proposed—45 FR 77341, § 772.122-2.
FIFRA, section 3: Proposed—43 FR 29710, § 163.61-8(3) and 43 FR 29712 (Appendix).

(b) *Boiling point/boiling range.* (1) Contribution to risk assessment. The boiling point of a liquid is the temperature at which its vapor pressure equals the pressure of its surrounding environment. Data on boiling point/boiling range are useful for chemical fate and exposure analysis because they indicate the physical form of the substance at ambient temperatures. A boiling point near ambient temperatures indicates the possibility of vaporization of the substance, with concommitant possibility of exposure by inhalation. These data are also useful for identification purposes, and may contribute to the design of other tests of the chemical.

(2) Test protocols and estimated cost.
OECD: Estimated cost of test—$50.
IRLG: None.
TSCA, section 4: In preparation
FIFRA, section 3: Proposed—43 FR 29710, § 163.61-8(9) and 43 FR 29712 (Appendix).

(c) *Density of liquids and solids.* (1) Contribution to risk assessment. Density is the mass per unit volume of a chemical substance at a specified temperature. Data on density is useful for assessment of chemical transport and fate because it indicates whether immiscible, low-reactivity chemicals will tend to sink or float when released into water.

(2) Test protocols and estimated cost.
OECD: Estimated cost of test—$50.
IRLG: None.
TSCA, section 4: Proposed—45 FR 77338, § 772.122-1.
FIFRA, section 3: Proposed—43 FR 29710, § 163.61-8(8) and 43 FR 29712 (Appendix).

(d) *Vapor pressure curve.* (1) Contribution to risk assessment. Vapor pressure values indicate the tendency of pure substances to vaporize and thus provide an indication of the relative volatilities of chemical substances. Volatility is an important consideration in assessing chemical fate and potential for exposure, because volatization may lead to dispersal of an uncontained chemical substance over wide areas. Also the vapor pressure can be useful in deciding whether to conduct a photochemical degradation test.

(2) Test protocols and estimated cost.
OECD: Estimated cost of test—$300.
IRLG: None.
TSCA, section 4: Proposed—45 FR 77345, § 772.122-3.
FIFRA, section 3: Proposed—43 FR 29710, § 163.61-8(10) and 43 FR 29712 (Appendix).

(e) *Water solubility.* (1) Contribution to risk assessment. The water solubility of a chemical is an important parameter determining its environmental transport and distribution. In general, highly soluble chemicals are more likely than poorly soluble chemicals to be distributed by the hydrologic cycle. In addition, water solubility can affect adsorption and desorption on soils and volatility from aquatic systems, as well as possible transformation by hydrolysis, photolysis, oxidation, reduction, and biodegradation in water. Also, knowledge of water solubility is needed for the design of most chemical tests and many ecological and health tests. Water solubility also affects uptake by humans and other living organisms.

(2) Test protocols and estimated cost.
OECD Estimated cost of test—$300.
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: Proposed—43 FR 29710, § 163.61-8(4) and 43 FR. 29712 (Appendix).

(f) *Octanol/water partition coefficient.* (1) Contribution to risk assessment. The octanol/water partition coefficient, P, is the ratio of the equilibrium molar concentrations of a chemical substance in octanol and

water. Accumulation and transport of a chemical substance in a living organism are governed by polarity, water solubility, affinity for fatty tissues, and the nature of potential binding to biological receptors. The octanol/water partition coefficient measures the relative equilibrium distribution of a substance between the fat and water phases of the test system. It therefore serves as an indicator of bioconcentration potential in fatty tissues and of the ability to pass through all membranes. Bioconcentration potential is an important factor in assessing chemical risk. In conjunction with data on chemical persistence, bioconcentration potential may be used to identify chemicals which may be transported via food chains.

(2) Test protocols and testimated cost.
OECD: Estimated cost of test—$250.
IRLG: None
TSCA, section 4: Proposed—45 FR 77350, § 772.122–4.
FIFRA, section 3: Proposed—43 FR 29710, § 163.61–8(6) and 43 FR 29712 (Appendix).

(g) *Hydrolysis (as a function of pH).* (1) Contribution to risk assessment. Hydrolysis can be an important phenomenon in determining the persistence of a chemical substance in the environment. Chemical substances may undergo hydrolysis and be transformed into new substances with properties different from their precursors. The importance of these transformations of chemcials as dominant pathways in aqueous media can be determined quantititatively from data on hydrolysis rate constants.

(2) Test protocols and estimated cost.
OECD: Estimated cost of test—$250.
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: Proposed—43 FR 29717, § 163.62–7(b) and 43 FR 29721 (Appendix).

(h) *Spectra (UV and visible).* (1) Contribution to risk assessment. The ultraviolet and visible light absorption spectra of chemical substances in solution are important physical properties that are characteristic of molecular structure. Spectral data can give indications of the wavelenghts at which photochemical degradation of the chemical may occur. Such data are therefore useful for determining the need for further testing of persistence in the atmosphere or aquatic environment.

(2) Test protocols and estimated cost.
OCED: Estimated cost of test—$200.
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: Proposed—43 FR 29710, § 163.61–7(b)(2) and 43 FR 29712 (Appendix).

(i) *Soil adsorption/desorption.* (1) Contribution to risk assessment. The affinity of a chemical substance for particulate substances is an important factor affecting its environmental movement and ultimate fate. Substances that adsorb tightly to soil particles may be less subject to environmental transport in the gaseous phase or in solution. On the other hand, high adsorptivity to soil particles may increase environmental transport with windblown dust or eroding soil; high adsorptivity may also lead to accumulation of the substance in the soil.

(2) Test requirements and/or protocols and estimated cost.
OECD: Estimated cost of test—$2,000.
IRLG: None.
TSCA, section 4: Proposed—45 FR 77352, § 772.122–5.
FIFRA, section 3: Proposed—43 FR 29716, § 163.62–5(c) and 29719 § 163.62–9(d) and 29721 (Appendix).

(j) *Dissociation constant.* (1) Contribution to risk assessment. The dissociation characteristics of a chemical are important for risk assessment because they govern the form in which the chemical exists. This, in turn, determines its chemical behavior and transport characteristics. Dissociation also affects adsorption onto soil particles and sediments and movement into and out of living cells.

(2) Test protocols and estimated cost.
OECD: Estimated cost of test—$150.
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: None.

(k) *Particle size distribution.* (1) Contribution to risk assessment. Particle size distribution affects the probability of human inhalation or ingestion of a limited sub-class of particulates as well as the likely point of their deposition in the respiratory tract. It also influences the distribution of a particle in the environment. Accordingly, the data element which describes particle size is important because it identifies potential health hazards arising from human inspiration due to direct exposure and provides information on the transportation and sedimentation of particulates in water and air.

(2) Test protocols and estimated cost.
OECD: Estimated cost of test—$100.
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: None.

2. *Ecotoxicology.* (a) *Acute toxicity to fish.* (1) Contribution to risk assessment. Data on a chemical's toxicity to fish are important because of the substantial value of commercial and recreational fishing and the essential functional role of fish in aquatic food chains. These studies provide data to determine the median lethal concentration (LC_{50}) of a chemical substance for fish, and permit estimation of the chemical's toxicity to a vertebrate species relative to that of other chemicals. This estimation of relative toxicity contributes to the assignment of priorities for further testing. In addition, acute toxicity tests may provide guidance for subsequent chronic testing.

(2) Test protocols and estimated cost.
OECD: Estimated cost of testing—$1,250 (includes LC_{50}, rangefinding test, and analytical assay).
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: Proposed—43 FR 29734, § 163.72–1.

(b) *Growth inhibition study, unicellular algae.* (1) Contribution to risk assessment. Testing for inhibition of the growth of algae indicates the extent to which a chemical substance can affect primary producers in lakes, streams, estuaries, and oceans. This testing provides data from which threshold toxicity values can be determined and positioned relative to other chemicals. This study can also generally indicate growth stimulation as well as growth inhibition. Algae are particularly important as test organisms among plants because they constitute the major mechanism for fixation of energy in most aquatic environments.

(2) Test protocols and estimated cost.
OECD: Estimated cost of testing—$1,450 (includes IC_{50}, rangefinding test and analytical assay.)
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: None.

(c) *Daphnia* reproduction study (3 broods). (1) Contribution to risk assessment. Daphnia provide important data for risk assessment because they are very sensitive to toxic substances and serve in the base set as a representtive of invertebrate species. This life-cycle study permits a more complete evaulation of potential hazard from chronic exposure to a chemical through the different life stages and functions of the organism.

(2) Test protocols and estimated cost.
OECD: Estimated cost of testing—$1,400 (includes reproduction test rangefindings test and analytical assay.)
IRLG: None.
TSCA, section 4: In preparation.
FIFRA, section 3: None.

3. *Degradation/Accumulation.* (a) *ready biodegradability.* (1) contribution to risk assessment. Biodegradation is the predominant mechanism for mass transformation of orgnic compounds in soil and water. Biodegradation data

permits a more realistic prediction of the chemical's environmental concentration, which is essential to an adequate assessment of its risk to the environment.

Biodegradation is also the most important degradative mechanism for organic compounds with respect to extent degradation; photochemical to chemical degradation and other processes usually do not completely mineralize organic substances. The form of a chemical which is most prevalent in the environment is an important aspect of risk. Accordingly, knowledge of the extent of a chemical's potential to biodegrade is necessary to determine the environmental fate of a chemical. It is also essential to assess the risk posed by the chemical to the environment.

Testing for ready biodegradability also contributes to risk assessment by providing a preliminary indication of the test substance's effect on mocroorganisms. Moreover, these data can indicate the potential effects of a new chemical on the microbial population and thus on the effectiveness of a secondary sewage treatment plant.

(2) Test protocols and estimated cost.

OECD: Estimated cost of test—range of $250 to $9,000 (depending on which of several tests is selected).

Note.— The OECD Expert Group on Degradation/Accumulation has identified five candidate tests for assessing "ready biogradability," and has provided guidance for selecting the appropriate test for various types of chemicals.

IRLG: None.

TSCA, section 4: In preparation.

FIFRA, section 3: Proposed—43 FR 29716, § 163.62–7 and 29720 § 163.62–11.

(b) *Bioaccumulation* (uptake from medium). (1) contribution ot risk assessment. The tendency to bioaccumulate enables chemical substance to cause toxic injury and alter ecological processes at concentrations much lower than those predicted from acute and subacute studies. Moreover, it enhances the chemical's ability to affect life far removed from the initial points of entry into the environment. More indirect effects can occur when a chemical which is highly accumulative contaminates organisms like fish to the extent that they are unsafe or undesirable to consumers.

Preliminary screening data is necessary to distinguish chemcial substances with low or moderate bioaccumulative character from those with high bioaccumulative character. This information will be used in conjunction with data on toxicity, transport, and fate of a chemical to assess the risk resulting from the release of that chemical into the environment.

(2) Test protocols and estimated cost.

OECD: There are two OECD base set bioaccumulation tests: bioconcentration in marine organisms (estimated cost $850) and static bioaccumulation in fish (estimated cost $2,000).

IRLG: None.

TSCA, section 4: In preparation.

FIFRA, section 3: 43 FR 29720, § 163.62–11.

4. *Toxicity Studies For Human Health Effects.* (a) *Acute Toxicity: Oral, dermal, and inhalation.* (1) Contribution to risk assessment. Acute toxicity studies must be determined to assess the potential risk of poisoning by a single exposure to a new chemical. These studies provide data to determine the median lethal dose (LD_{50}) of a chemical substance and permit estimation of the toxicity of this substance relative to that of other chemicals. They may also provide data to approximate its mode(s) of action, to determine its specific toxic effect(s) on target organs and functions, and to determine any difference in sensitivity to this substance among species or routes of exposure.

(2) Test protocols and estimated cost.

OECD: Estimated cost of tests—Acute Oral Toxicity $2,000; Acute Dermal Toxicity $2,800; Acute Inhalation Toxicity $3,300.

IRLG: 44 FR 49015 (announces availability of draft guidelines from Industry Assistance Office)

TSCA, section 4: (i) Acute Oral Toxicity-Proposed—44 FR 44066, § 772.112–21; (ii) Acute Dermal Toxicity-Proposed—44 FR 44067, § 772.112–22; (iii) Acute Inhalation Toxicity-Proposed—44 FR 44067, § 772.112–23.

FIFRA, section 3: (i) Acute Oral Toxicity-Proposed—43 FR 37355, § 163.81–1; (ii) Acute Dermal Toxicity-Proposed—43 FR 37356, § 163.81–2; (iii) Acute Inhalation Toxicity-Proposed—43 FR 37357, § 163.81–3.

(b) *Primary dermal irritation/corrosion.* (1) Contribution to risk assessment. Data from a primary dermal irritation study indicate the capacity of a chemical to cause irritation and/or corrosion effects on the skin of laboratory animals. This evaluation can be used to guide health and safety practices for the handling of a chemical substance.

(2) Test protocols and estimated cost.

OECD: Estimated cost of test—$700.

IRLG: None.

TSCA, section 4: Proposed—44 FR 44071, § 772.112–25.

FIFRA, section 3: Proposed—43 FR 37360, § 163.81–5.

(c) *Primary eye irritation/corrosion.* (1) Contribution to risk assessment. Data from a primary eye irritation study indicate the capacity of a substance to produce injury to the eye and associated mucus membranes. Evaluation of this potential hazard can be used to guide health and safety practices for the handling of a chemical substance.

(2) Test protocols and estimated cost.

OECD: Estimated cost of test—$450.

IRLG: 44 FR 49015.

TSCA, section 4: Proposed—44 44070, § 772.112–24.

FIFRA, section 3: Proposed—43 FR 37359, § 163.81–4.

(d) *Skin sensitization.* (1) Contribution to risk assessment. Data from dermal sensitization studies indicate the capacity of a chemical to induce a state of delayed contact sensitization when it comes in contact with the skin of laboratory animals. The evaluation of a chemical for potential skin sensitizing hazard can be used to guide health and safety practices for the handling of a chemical substance.

(2) Test protocols and estimated cost.

OECD: Available in 1981. Estimated cost of test—range of $3,200 to $6,700 (depending on which method is selected)

IRLG: None.

TSCA, section 4: Proposed—44 FR 44071, § 772.112–26.

FIFRA, section 3: Proposed—43 FR 37361, § 163.81–6.

(a) *14–28 day repeated dose.* (1) Contribution to risk assessment. Repeated dose toxicity studies are performed to determine dose-respone relationships and major organ toxicity associated with repeated exposure to a test substance. Repeated dose information is also of fundamental importance in cost effectively designing expensive subchronic or chronic toxicity studies with much longer exposure periods.

(2) Test protocols and estimated cost.

OECD: Available in 1981. Estimated cost of test—$10,200–12,800.

IRLG: None.

TSCA, section 4: Proposed—44 FR 44072, § 772.112–31.

Note.—The TSCA protocol calls for a minimum 90-day study on a rodent and non-rodent species.

FIFRA, section 3: Proposed—43 FR 37363, § 163.82.

Note.—The FIFRA protocol calls for a minimum 90-day study of a rodent and non-rodent species.

(f) *Mutagenicity.* (1) Contribution to risk assessment. Data from mutagenicity studies may indicate the capacity of a substance to produce alterations (mutation) in the genetic materials of a

cell either at the gene or chromosome level. Such mutations may result in teratogenic or carcinogenic effects in exposed persons, as well as mutagenic effects that are transmitted to future generations. Since some chemicals induce only one genetic alteration, studies for both gene (point) mutations and chromosomal aberrations are needed in the basic screening step. The preferred test for gene mutations is the *S. typhimurium* reversal mutation assay (Ames test). The *E. coli* WP2 reverse mutation assay may be substituted if this system is likely to be more sensitive to the test chemical. While an *in vitro* mammalian cytogenetics test is preferred in testing for chromosome aberrations, an *in vivo* mammalian cytogenetics test may be substituted where a scientific rationale exists.

(2) Test protocols and estimated cost.

OECD: Estimated cost of tests. (i) *Gene Mutations-S. typhimurium* Reverse Mutation Assay—$1,000; *E. coli* WP2 Reverse Mutation Assay—$350. (ii) *Chromosome Aberrations-In vitro* mammalian cytogenetics test $3,000; *In vivo* mammalian bone marrow cytogenetics test; $13,000 Micronucleus test—$2,000.

IRLG: None.

TSCA, Section 4: Proposed—44 FR 44054, § 772.114–1—772.114–4.

FIFRA, Section 3: Proposed—43 FR 37388, § 163.84–1—163.84–4.

Dated: January 19, 1981.

(15 U.S.C. 2601 et seq.)

Douglas M. Costle,

Administrator.

[FR Doc. 81–2851 Filed 1–26–81; 8:45 am]

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40 CFR Part 772

[OPTS–46007A; TSH FRL 1593–3–1594–4; TSH–FRL 1720–1a]

Environmental Test Standards: Clarification of Policy; Extension of Time for Comment and Rescheduled Meeting

AGENCY: Environmental Protection Agency (EPA).

ACTION: Extension of time for comment.

SUMMARY: This notice extends the comment period and reschedules the related meeting, open to the public, to receive oral comment for the Agency's proposal of certain environmental test standards published in the Federal Register on November 21, 1980 at (45 FR 77332). This notice also gives a clarification of policy respecting that proposal's preamble discussion of these standards' relationship to international guidelines, particularly those being developed through the Organization for Economic Cooperation and Development (OECD).

DATES: Written comments should be submitted on or before Monday, March 16, 1981. The opportunity to present oral comments in an open meeting has been rescheduled to Tuesday, March 31, 1981, 1:00–5:00 p.m. The previously announced meeting for February 10th is hereby canceled. See below for further details on this open meeting.

ADDRESSES: Written comments should bear the EPA document control number (OPTS–46007A) and should be submitted to: Document Control Officer (TS–793), Management Support Division, Office of Pesticides and Toxic Substances (OPTS), Environmental Protection Agency, Room E447, 401 M St., SW, Washington, D.C. 20460, (202–755–8050).

See Supplementary Information, Extension of Time for Comment for location of the open meeting.

FOR FURTHER INFORMATION CONTACT: John B. Ritch, Jr., Director, Industry Assistance Office (TS–799), Office of Pesticides and Toxic Substances, Environmental Protection Agency, Room E427, 401 M St., SW, Washington, D.C. 20460, Toll free: (800–424–9065); in Washington, D.C.: (202–554–1404).

SUPPLEMENTARY INFORMATION:

I. Background

The Agency is proposing a series of generic standards for development of test data to have available for incorporation in specific chemical testing rules as they are issued under section 4 of the Toxic Substances Control Act (TSCA). The authority for these proposals is TSCA, Pub. L. 94–469; 90 Stat. 2006; 15 U.S.C. 2603. Previously published proposals covered the development of data on chronic health effects and Good Laboratory Practices for health effects (May 9, 1979, 44 FR 27334), and also on acute and subchronic toxicity, mutagenic, teratogenic and reproductive effects and metabolism studies (July 26, 1979, 44 FR 44054). On November 21, 1980 (45 FR 77332) the Agency proposed standards for development of test data on certain physical and chemical characteristics of substances and Good Laboratory Practices related to environmental effects testing. The notice covered testing for Density/Relative Density, Melting Temperature, Vapor Pressure, Octanol/Water Partition Coefficient and Soil Thin Layer Chromatography. In the future the Agency will be proposing additional test standards for neurobehavioral toxicity, other physical, chemical and environmental persistence characteristics and various ecological effects.

In the preamble to the November 21st proposal (45 FR 77335) the Agency discussed the relationship of TSCA test standards to interagency and international test guidelines. Since then, the Agency has been requested to clarify this relationship, in particular with respect to its activities within the framework of the Organization for Economic Cooperation and Development (OECD). The clarification of policy below addresses this concern.

II. Clarification of Policy: Relationship to International Guidelines

In proposing these requirements, EPA recognized its obligations under Title IV of the Trade Agreements Act of 1979 (Pub. L. 96–39). That law provides the legal framework for implementing trade agreements entered into by the United States. Title IV (the Standards Code), by setting forth principles and procedures for Federal agencies, including EPA, to follow in rulemaking, aims at preventing the creation of unnecessary technical barriers to foreign trade.

As stated in section 401, the Standards Code is not intended to prevent Federal agencies from making rules or setting standards affecting international trade, for example, in chemical products, if such measures have as a demonstrable purpose the achievement of a legitimate domestic objective, such as protecting health, safety or the environment within the United States, and do not operate to exclude imported products which fully meet the objectives of such measures. Title IV states, however, that agencies involved in such rulemaking shall consider the adoption of existing international standards, if they are appropriate, and shall ensure that imported products are treated no less favorably than like domestic or other imported products.

As noted in the earlier Federal Register notice, the U.S. EPA has been a full and regular partner in extensive international consultations and negotiations in the OECD during the development of its chemical testing and other requirements under TSCA. The Agency places a high priority on these activities because of benefits both for international chemical trade and for more effective health and environmental protection.

U.S. experts, along with those of other OECD member states, have worked since 1977 to develop agreed chemical testing guidelines and good laboratory practices, as well as an agreed set of data that should be developed for new chemicals prior to marketing. The